PROTOCOL TITLE: Exercise and markers of medial temporal health in youth at ultra high-risk for psychosis, Phase 2

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Objectives

Based off of the success of the feasibility study completed at our University of Colorado Boulder lab named "Exercise and markers of medial temporal health in youth at ultra high-risk for psychosis" (protocol #14-0200), we have moved on to the second phase of the study, which is named the R33 phase. The goals of this study are to continue to look at the effectiveness of a cardiovascular exercise in promoting brain health and improving related symptoms (e.g. hearing sounds that are not there, feeling emotionally detached from self and others), cognitive difficulties (troubles with memory and learning), and every day social-occupational functioning in youth at imminent risk for developing a psychotic disorder such as schizophrenia. We call this population "Ultra High Risk (UHR)" or "Prodromal". Usually these individuals have a cluster of symptoms called positive symptoms that characterize what the field calls "Thought Disorder." Please see below and under "Background and Significance" for further discussions of UHR.

"Ultra High-Risk" or "Prodromal" is the term that has been chosen by the field to describe individuals who may be experiencing symptoms that make them at risk for developing a psychotic illness such as schizophrenia, bipolar disorder with psychotic features, clinical depression with psychotic features. Thought disorder is characterized by unusual thoughts, suspiciousness/paranoia, a sense of having special powers or unrealistic plans for the future, and/or unusual experiences with seeing or hearings things that are not there.

We currently have been working with this population for four years in our "Frontal-Subcortical Development, Movement Abnormalities, and Risk for Psychosis" study as well as our phase one study mentioned above, protocol 14-0200 at the University of Colorado Boulder before Professor Dr. Vijay Mittal became a new faculty member this year at Northwestern University. We will continue to use a measure called the Structured Interview for Prodromal Symptoms (SIPS), a widely used and well validated symptom measure, to see if a person is showing moderate attenuated positive symptoms (indicated by a score of a 3, 4, or 5 on positive symptoms of this scale) and a global decline in functioning which would make them UHR or prodromal.

The study follows adolescents and young adults who may have a thought disorder and who may be at risk for developing psychosis.

Understanding how exercise may protect or improve the health of a brain area that is implicated as a major contributing factor to the onset of psychosis may lead to a path-breaking new intervention that does not suffer from many of the side effects, costs, and other barriers that characterize treatments that are currently available for this group. Because a significant portion of high-risk youth go on to develop a psychotic disorder in a short period, intervening at this stage may help to improve the clinical course and ultimately prevent the onset of a devastating and prevalent mental illness.

Specific Aim 1) If UHR subjects participating in the exercise condition show greater post-trial increases in medial temporal volume and improved cognitive, symptom and social/role functioning profiles when compared with the UHR waitlisted-controls. We predict that the UHR exercise treatment group will show a strong trend to suggest larger effects for increases in hippocampal and parahippocampal gyral volume, and improvements in cognitive,

social/functional, and symptom profiles after the trial as compared to the UHR waitlist controls. Any naturalistic aerobic activity seen in the UHR waitlisted-controls will be monitored by testing for changes in aerobic fitness between the pre-post 12-week assessments (although we do not anticipate a great deal of naturalistic aerobic activity in the UHR control group based on our pilot findings, any changes in fitness will be controlled for in the respective statistical analyses)

Exploratory: Aim A) If the intervention has an influence on course of illness and conversion rates. An important ultimate consideration for UHR individuals relates to clinical outcome or conversion to formal psychotic disorders. Within-group analyses will focus on how varying degrees of aerobic fitness, brain, and cognitive changes post trial or wait-list predicts 12-month and 24-month symptoms levels and conversion status.

Background

Accumulating evidence from animal models (Wolf et al., 2011), healthy populations (Erickson et al., 2011), and schizophrenia studies (Farrow et al., 2005) suggests that regular exercise positively affects integral functions such as neurological maintenance and cognition. Likewise, moderate to vigorous activity has been associated with improved quality of life and lower symptom levels in patients with schizophrenia (Gorczynski & Faulkner, 2010). Because voluntary exercise has been found to stimulate adult medial temporal neurogenesis (Parker et al., 2011), and the hippocampal and parahippocampal gyrus abnormalities have been widely observed in structural, functional, and neurocognitive studies of schizophrenia (Wible et al., 1995, Walker et al., 2008, Allen et al., 2011), aerobic physical activity may be an important treatment in schizophrenia. The period immediately preceding the onset of schizophrenia is a viable point for intervention, and a critical phase for elucidating the pathophysiology of the disorder. However, the available interventions have not been definitely effective, and these treatments have been met with significant challenges including costs, poor compliance, attrition, and side effects. A new series of cognitive remediation trials promoting neuroplasticity have shown a great deal of potential for targeting specific symptoms and characteristics (Barlati et al., 2012). Despite the promise of exercise interventions in animal models as well as both healthy and clinical populations, to date there have been no trials in youth at ultra high-risk (UHR) for psychosis. We propose an initial within-subject study to determine the effects of a 12-week exercise trial, comparing two different levels of exercise intensity in targeting specific neural, cognitive, symptom, and social/role function outcomes in UHR youth.

The Prodromal Period and Research Priorities

The onset of psychosis is usually preceded by a prodromal phase characterized by functional decline and subtle attenuated symptoms that include positive phenomena and a decline in socio-occupational functioning (Haroun et al., 2006, Cannon et al., 2008). The prodromal period is of interest both as a window for investigating processes involved in disease onset, and also as a potential point of intervention and prevention (Haroun et al., 2006, McGlashan et al., 2007, Mittal et al., 2010b). More specifically, recent studies have suggested that adolescents with a prodromal syndrome (i.e., showing moderate attenuated positive symptoms accompanied by a global decline in functioning) (Miller et al., 1999, Miller et al., 2002, Miller et al., 2003b) are at imminent risk for conversion to a psychotic disorder; although successful early identification and other factors relating to heterogeneous assessment/inclusion criteria have yielded a global decrease in transition rates (Yung et al., 2007), a substantial proportion (anywhere from 10-35%)

will convert to a psychotic disorder within a two-year period (Yung et al., 2007; Cannon et al., 2008). This is promising from a research perspective as prospective understanding of brain structure and function, in a period prior to when medications and neurotoxicity can confound research, is likely to significantly inform etiological conceptualizations of psychosis (Haroun et al., 2006, McGlashan, 2006). It is also significant from a clinical perspective as better understanding of the high-risk period will help to implement early intervention and guide treatment decisions with the potential to reduce the duration of untreated psychosis (White et al., 2006), ameliorate course of illness, and delay or potentially prevent onset of psychosis (McGorry et al., 2002, McGlashan et al., 2003, Woods et al., 2003, Morrison et al., 2004, Haroun et al., 2006). Because schizophrenia severely limits the most productive years of an individual's life, its costs to society are enormous (Wu et al., 2005), and this promise of early detection and intervention represents a major breakthrough.

While existing cognitive-behavioral (Morrison et al., 2004), psychopharmacological (McGlashan et al., 2003, McGlashan et al., 2007), and supplemental treatments (Amminger et al., 2010) have shown noteworthy effects, to date there have been no conclusive empirically supported interventions for UHR youth (Corcoran et al., 2010). Furthermore, there are significant treatment costs associated with psychotherapy, and serious adverse side effects accompanying pharmacological interventions (e.g. weight gain, related diabetes) (Gerbino-Rosen et al., 2005, Sporn et al., 2005). There is a critical need for innovative new treatment options. Recent cognitive remediation trials in psychosis have demonstrated benefits from neuroplasticity based interventions and that intensive trials engaging effortful activity are feasible in UHR samples (Fisher et al., 2013). Because of its known effects on neuroplasticity, an exercise-based intervention holds significant potential as UHR youth show abnormalities in medial temporal structures as well as related cognitive impairments, symptoms and functional factors (Pantelis et al., 2007, Mittal & Walker, 2009, Walker et al., 2010, Mittal & Walker, 2011b, Mittal et al., 2013).

Mechanisms of Cardiovascular Exercise on Medial Temporal Health

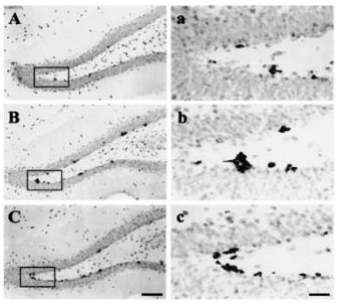


Figure 1. Photomicrographs of 5-bromo-2′-deoxyuridine (BrdU)-positive cells in the hippocampus (dentate gyrus). A and a, control group; B and b, easy exercise group; C and c, moderate exercise group. Black dots represent BrdU-positive cells. Scale bar in A, B, and C represents 100 μm. Scale bar in a, b, and c represents 12.5 μm.

Animal models have been instrumental in establishing the effects of aerobic activity on medial temporal health. This body of literature has suggested that aerobic activity promotes hippocampal growth and related function through several processes including promoting neurogenesis (process by which neurons are generated from neural stem and progenitor cells) (Cotman & Berchtold, 2002, Wolf et al., 2011), cell proliferation (increase in the number of cells as a result of cell growth and cell division) (Koehl et al., 2008) and slowing apoptosis (programmed cell death) (Avula et al., 2001, Phaneuf & Leeuwenburgh, 2001). For example, in an animal study examining the effects of treadmill exercise on cell proliferation in the hippocampus (dentate gyrus), Sprague-Dawley rats were classified into controls, an easy exercise group, and a moderate exercise group (Kim et al., 2002). Results suggested a dose dependent response where easy and moderate exercise group rodents exhibited significant cell proliferation (increase in BrdU-positive cells) in the dentate gyrus compared to controls after 30 minutes of exercise a

day for one week (see Figure 1). Research also shows that exercise and fitness level can significantly alter blood oxygen level dependent (BOLD) activation in the parahippocampal gyrus (Janse Van Rensburg et al., 2009, Holzschneider et al., 2012), a grey matter cortical region that encapsulates the hippocampus and plays an integral role in memory coding and retrieval. Further, exercise-related brain plasticity has been shown in the increased temporal lobe connectivity between the bilateral parahippocampal gyrus and bilateral medial temporal gyrus in older adults (Voss et al., 2013). With regard to the current proposal, its is important to note that several animal models have suggested that an aerobic exercise program promotes neuroplastic changes in the hippocampal formation (e.g., significant increase of protein level in the hippocampal formation and PV-immunoreactive neurons in CA1 and CA2/CA3) during adolescent period (Gomes da Silva et al., 2010).

Accumulating evidence from a series of translational studies has indicated that the pattern of results seen in the animal research is also true for human populations. For example, aerobic exercise has been found to result in increased hippocampal blood volume in healthy individuals (Colcombe et al., 2004). There have also been several venues of research to suggest exercise counteracts declining medial temporal function in aging (Intlekofer & Cotman, 2012) and clinical populations such as those with Alzheimer's disease (Yuede et al., 2009, Erickson et al., 2011). To date, there have been a small number of studies showing positive effects from exercise that are also seen in schizophrenia patients. For example, researchers observed naturalistic activity levels over a 20-hour period (actigraphy) were positively associated with larger cortical volumes (Farrow et al., 2005). In a landmark study, Pajonk and colleagues (Pajonk et al., 2010) found that after a brief cardiovascular exercise trial (12 weeks) in patients diagnosed with schizophrenia, those in the exercise group showed a significant increase in hippocampal volume (12%) when compared to a control group of schizophrenia patients in a non-aerobic activity (1%). Further, the changes in volume were positively associated with improvement in aerobic fitness (measured by a change in maximum oxygen consumption) and improvement in verbal memory. However, its important to note that while this work was instrumental in demonstrating trial-feasibility and a potentially effective treatment mechanism, the sample was small, analysis of structure involved a gross volume estimate (no consideration of shape), and the study included only a limited cognitive battery.

Exercise and Cognitive Function

There is good evidence to suggest that hippocampal neurogenesis is an important mechanism for learning and memory processes in healthy humans. There have been several proposed mechanisms for explaining the relationship between increased neurogenesis and improved cognition, including computational theories demonstrating that new neurons improve memory capacity (Becker, 2005), reduce interference between memories (Wiskott et al., 2006), and add information about time to memories (Aimone et al., 2006). The act of learning itself is associated with elevated neuronal survival (Gould et al., 1999). Exercise has been found to improve cognitive functioning by promoting synaptic plasticity through a series of mechanisms that contribute to neuroreorganization processes (allowing neurons and respective networks to change connections and behavior in response to new information, stimulation, development, damage and dysfunction). For example, research has shown that capacity of synaptic plasticity (the ability of the connection between two neurons to change in strength in response to either use or disuse of transmission over synaptic pathways) (Hughes, 1958) is positively associated with

aerobic activity; rats given access to a running wheel (aerobic exercise) exhibit significantly more short-term potentiation and long-term potentiation (LTP) with theta-patterned conditioning stimulation in vivo than do age-matched litter mate controls (Farmer et al., 2004). This increase in LTP appears to reflect an alteration in the induction threshold for synaptic plasticity that accompanies voluntary exercise (Farmer et al., 2004). With particular relevance to the proposal, researchers have found that regular aerobic exercise (30 minutes of aerobic exercise for regular sessions over 8 weeks) increases the number of hippocampal CA1, CA3, and dentate gyrus neurons and enhances spatial memory in adolescent rats (Uysal et al., 2005).

In a recent comprehensive review of the literature, researchers concluded that although more high-quality trials are needed to assess the effects of different types and intensities of exercise on cognitive function, beneficial effects of various exercise programs have been observed in studies among subjects with and without cognitive decline (van Uffelen et al., 2008). Studies have shown cognitive improvements in Alzheimer's patients (Kramer et al., 2006) and after an 8 week exercise trial, stroke survivors (stationary bike, 3 times a week for 45 minute sessions) showed significant improvement in VO2max (i.e., a widely used and accurate index of aerobic fitness), and cognitive function (Quaney et al., 2009). As noted, a trial in patients with schizophrenia found improvements in verbal learning (Pajonk et al., 2010), an important process that is also affected in UHR groups (Brewer et al., 2005). Several of the other neurocognitive deficits present in UHR individuals have also been positively affected by exercise interventions in other populations. A large randomized controlled study with 120 individuals showed that exercise training increases the size of the anterior hippocampus and led to improvements in spatial memory in older adults (Erickson et al., 2011) and both this brain region and memory domain are affected in the prodrome (Wood et al., 2003, Pantelis et al., 2007). This has been supported by the animal literature (rodent models) (Vaynman et al., 2004) and observed in investigations of healthy young adults (Stroth et al., 2009). Hippocampal-dependent cognitive functioning such as the acquisition of new episodic memory is mediated in part by synaptic plasticity (Neves et al., 2008) and also found to be improved in exercise trials in humans (Bunce & Murden, 2006). Episodic memory deficits are also prominent in UHR youth (Valli et al., 2012). The medial temporal memory system (including the hippocampus and parahippocampal gyrus) governs broader declarative memory functions including episodic memory as well as verbal learning (Squire, 1992); as noted a successful trial in a small number of schizophrenia patients showed significant verbal learning improvement (Pajonk et al., 2010), and deficits in the verbal learning domain are both prominent in the prodrome (Fusar-Poli et al., 2012) and predictive of conversion (Walder et al., 2008, Mittal et al., 2010c, Seidman et al., 2010). The cognitive targets in this proposal are based on the domains that have reliably been shown to be improved with exercise intervention in human populations, known to recruit heavily on medial temporal structures, and shown to be affected in UHR youth (i.e., spatial memory, episodic memory, verbal learning). In addition, because of the central role medial temporal structures play in a wide range of high order cognitive functions (Voss et al., 2010), some research has shown exercise promotes improvements in domains such as executive function, although the specificity of this effect remains an empirical question.

Exercise, Symptoms and Social/Role Functioning

Sedentary behavior has been widely associated with obesity and health problems in adolescent populations (Rosenberger et al., in press), and in addition to contributing to poor emotional well-being and peer-support (Costigan et al., in press), it may also exacerbate the health related side-effects of pharmacological treatment (Maayan & Correll, 2010) and potentially lead to poorer compliance in UHR adolescents. Further, the nature of the prodrome may contribute to sedentary activity as prototypic characteristic symptoms such as avolition affect motivation and positive symptoms such as paranoia may lead to avoidance of social/peer involved activities, leading these patients to become increasingly prone to inactivity. In contrast, moderate to vigorous activity has been found to have ameliorative effects, such as reduced cardio metabolic risk factors, regardless of the amount of time spent engaging in sedentary activities (Ekelund et al., 2012). More broadly, physical activity decreases the risk of numerous deleterious physical outcomes among adults (Penedo & Dahn, 2005) and adolescents (Janssen & LeBlanc, 2010), and sedentary behavior has been identified as one of the leading preventable causes of death in the United States (Mokdad et al., 2004). With regard to mental health, and consistent with studies in other populations (Dunn et al., 2001; Rangul et al., 2010), researchers have observed that exercise can improve symptoms of depression and social anhedonia in patients with schizophrenia (Gorczynski & Faulkner, 2010). As noted, to date there have been no studies to determine how exercise may improve symptoms and social/role functioning in UHR youth. Because of studies showing that an active lifestyle promotes higher quality of life, better mental health outcomes (Rangul et al., 2010), and lower rates of depression (Brunet et al., 2013) and anxiety (Hallal et al., 2006) in adolescents and young adults, we predict that the exercise trial will improve social and role functioning (Aims 2). Further, based on the prominent role of the medial temporal lobe in etiological theories of schizophrenia (Walker & Diforio, 1997, Lipska, 2002, Corcoran et al., 2003), and research noting significant relationships between the hippocampus and symptoms in psychosis (Benoit et al., 2012), we predict that aerobic exercise will also improve symptoms.

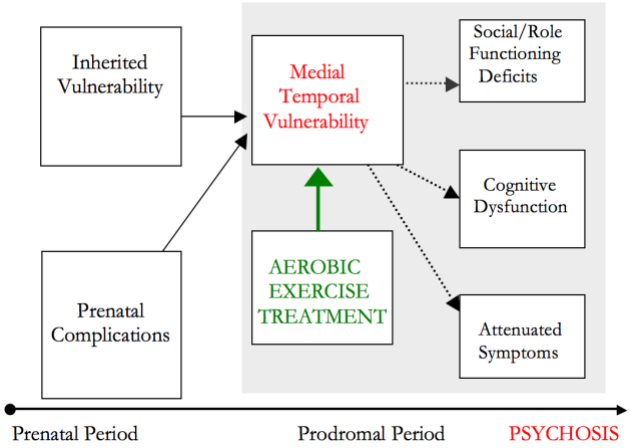
Cortisol Sampling

When accounting for the confluence of risk and disease progression in the prodromal period, a neural diathesis-stress model posits that one key pathogenic mechanism involves the hypothalamic pituitary adrenal (HPA) axis, which can trigger a cascade of events that culminates in expression of dysfunctional neural circuits that subserve psychotic symptoms (E. Walker, Mittal, & Tessner, 2008). This notion draws primarily on the extant evidence concerning the effects of HPA axis secretogues, especially cortisol, on brain and behavior. Specifically, patients at-risk for schizophrenia manifest elevated levels of cortisol, and there is a synergistic relationship between activation of dopaminergic circuits that have been implicated in psychosis (Czyrak, Mackowiak, Chocyk, Fijal, & Wedzony, 2003). It is also of note that normative increases in the stress hormone cortisol, beginning at the onset of puberty, peak at the end of adolescence and this coincides precisely with the mean age of onset of psychotic disorders (E. Walker, et al., 2008). However, although studies have examined resting cortisol, little is known about the effect of acute stress in the prodrome, or how this may constitute risk for a poorer course of illness over time (E. Walker, et al., 2008).

Research Questions

A neural diathesis-stress conceptualization is an established model used to understand pathogenic processes at play during the prodromal period and it predicts that an early vulnerability (the resulting confluence of genetic and/or early environmental factors) later interacts with neuromaturational processes and environmental stressors during adolescence, resulting in attenuated symptoms, cognitive and social/role dysfunction, and eventually psychosis (Walker & Diforio, 1997). Within the context of the present study, we propose to investigate the potential for an exercise intervention to promote medial temporal health in the high-risk period and subsequently influence a series of related symptoms and deficits (see Figure 2). If an exercise intervention is effective in promoting medial temporal health and facilitating synaptic plasticity in UHR youth, this can serve to improve several key features and characteristics strongly affected by hippocampal and parahippocampal gyral function including cognitive function, symptoms, and social/role function. To address the research questions posited in Aims 1 and 2, we propose to assess medial temporal integrity, cognitive function (with tests that weigh heavily on medial temporal function as well as a broader battery), social/role functioning, and symptoms both pre and post an exercise trial (with two intensity groupings) in a group of UHR youth and a healthy controls (HC) group.

Figure 2. Exercise Targets Key Pathogenic Factors Driving the Progression to Psychosis



Understanding the mechanisms and related effects of aerobic exercise in a developmentally sensitive period, characterized by significant neural-reorganization, symptom escalation, and cognitive functional decline, is both innovative and incredibly important. Further, examining the period immediately preceding the onset of psychotic disorder, before the medications and/or neurotoxicity can cloud our understanding (McGlashan, 2006), represents a necessary step in elucidate the etiology of psychotic disorders and increasing our ability to refine target interventions high-risk individuals. The proposed investigation holds promise for improving the understanding of aerobic activity based changes in medial temporal structures. A body of evidence suggests that aerobic exercise increases hippocampal volume in clinical and healthy populations (Yuede et al., 2009, Berle et al., 2010, Pajonk et al., 2010, Erickson et al., 2011, Wolf et al., 2011). Despite significant evidence to suggest medial temporal abnormalities in UHR youth (Fusar-Poli et al., 2007, Fusar-Poli et al., 2011, Mittal & Walker, 2011b), and prominent models implicating the hippocampus as an integral factor in the etiology of schizophrenia (Weinberger, 1995, Lipska, 2002, Corcoran et al., 2003, Walker et al., 2008), to date there have been no published studies that have examined an aerobic exercise mechanism in high-risk adolescents. We propose to use the most promising and innovative aerobic fitness assessments, structural imaging methodologies (including size and shape based approaches), and tailored neurocognitive tests to accomplish this goal.

Preliminary Studies

UHR Participants exhibit deficits in cognitive functioning and smaller medial temporal lobe volume

A group of UHR (n = 29) and healthy control (n = 27) adolescents (mean = 18.09; SD =2.3) were administered a structural scan and a brief cognitive battery. Consistent with the broader literature, the ANCOVA analyses (controlling for age) indicated that UHR group showed poor performance across cognitive measures including verbal fluency $F(1,50) = 2.25$, $p \leq .05$, trail making, $F(1,50) = 4.91$, $p \leq .01$, and a trend for verbal learning, $F(1,50) = 1.22$, $p = .14$, when compared to healthy controls. Analyses indicated that the UHR group showed significantly smaller right, $F(1,51) = 10.17$, $p \leq .01$, and left, $F(1,51) = 4.44$, $p \leq .01$, hippocampal volumes. Likewise, the UHR group showed a non-significant trend towards smaller left, $F(1,51) = .99$, $p = .18$, and significantly smaller right, $F(1,51) = 2.87$, $p \leq .05$, parahippocampal gyral volumes (see **Figure 3**). While these results serve to establish that cognitive and medial temporal lobe deficits are apparent in high-risk individuals, there has been little empirical work conducted to examine mechanisms that may contribute to these deficits, or interventions designed to target these specific domains. As noted in the review above, a body of evidence suggests that moderate to vigorous aerobic activity promotes hippocampal cell growth and memory in healthy and clinical populations.

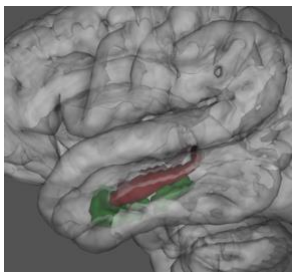


Figure 3. The volumes of the hippocampus (red) and parahippocampal gyrus (green) were found to be smaller in the high-risk group.

Less activity is associated with smaller medial temporal volumes and cognitive deficits

In this pilot investigation 29 UHR and 27 matched control participants were assessed to determine the relationship between naturalistic activity level (i.e., everyday behavior in a natural context that is not manipulated by instruction or intervention), medial temporal lobe structure (hippocampus and parahippocampal gyrus), and symptoms. Participants were assessed with actigraphy for a 5-day period (participants wore an actigraph wristwatch), magnetic resonance imaging, and structured interviews. We observed that UHR participants showed a greater percentage of time in sedentary behavior while healthy controls spent more time engaged in light, moderate and vigorous activity (**Figure 4**). In addition, the total level of movement activity was moderately correlated with parahippocampal gyri bilaterally (right: $r = .44$, $p \leq .01$; left: $r = .55$, $p \leq .01$), a trend towards volume of the left hippocampus ($r = .23$, $p = .09$) and symptoms ($r = -.35$, $p \leq .01$). The results suggest that more activity is linked to larger volumes and lower symptom levels. Furthermore, activity was associated with performance in verbal fluency $r = .35$, $p \leq .01$), trail making ($r = .28$, $p \leq .05$), and verbal learning ($r = .25$, $p \leq .05$). Taken together, these data indicate that more activity is associated with improved cognition or conversely, lower activity is linked to a poorer cognitive performance on these measures. Finally, hippocampal volumes were bilaterally associated with performance on trail making ($r = .27$, $p \leq .05$) and a trend toward verbal fluency ($r = .23$, $p = .08$).

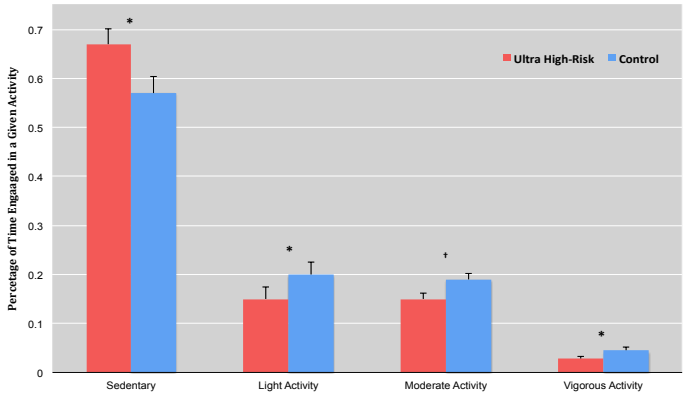


Figure 4. Note: Activity represents the percentage of time spent in four levels of activity based on actigraphy counts per minute. * $p \leq .05$; † Indicates a trend level difference $p \leq .15$; Error bars represent standard error.

I. While collectively, this pilot data is instrumental in suggesting that inactivity is associated with medial temporal health, symptoms, and cognition, it is not possible to determine any causality (for example, it is unclear if symptoms are driving inactivity, which in turn may be affecting the health of the parahippocampal structure or if hippocampal deficits lead to lower levels of activity). In our Aims, we propose to determine the optimal exercise prescription that balances intensity and tolerability in UHR youth, and whether prescribed physical activity will lead to changes in medial temporal volume, cognitive function and symptoms/function. An experimental manipulation, focusing an aerobic fitness and tailoring level of activity to an individual's initial level of cardiovascular fitness, will allow for stronger conclusions regarding the noted causality issue. Taken together, the Aims for this phase hold important implications for etiological conceptions and the promise of exercise-based interventions for UHR youth.

Inclusion and Exclusion Criteria

Participants will be recruited from community health care providers or self-referred by flyers, electronic and paper advertisements. Participants will call into the ADAPT lab and a lab manager or trained graduate student will administer a phone screening. Based off of the phone screening, participants and the inclusion criteria, participants will be invited to participate in the study based off of "being a good fit" for the study. A phone screening will also be done to determine if the participant is eligible for the MRI scanning portion of the study (i.e. inquiring about claustrophobia, metal in their body, etc...). If participants are found not to be eligible based off of the phone screening and inclusion criteria, then participants will be excluded.

If the participant is younger than the age of 18, and thus not considered an adult yet, a parent must call on (and this is indicated on recruitment material). The same phone screening will be completed with the parent and the questions will be about the child.

Inclusion criteria for UHR participants are as follows: a) age 16-24, b) no history of brain injury or neurological disease, c) no contraindications to exercise training (as assessed in the phone screening) d.) do not meet for any MRI scanning exclusion criteria as assessed via the phone screen. During the phone screening, we will assess to make sure there is not a history of cardiovascular or respiratory disease. During the exercise study, the participant's heart rate and EKG will be monitored to assure that they are not experiencing an adverse cardiac event and to assure they are healthy enough to participate. The phone screening will also assess to make sure the participant is not obese, pre-diabetic/diabetic, has high cholesterol, or has high blood

pressure, and does not have a diagnosis of current substance dependence (this will be determined in the phone screen). Participants will be asked if they ever had a history of substance dependence or if they currently are diagnosed with substance dependence. Additionally, during the clinical evaluation, they will be asked if they have a current diagnosis of substance dependence and other related questions during the SCID) and d) no contraindications for being in an magnetic resonance imaging (MRI) scanner. As noted above, for inclusion in the study, the at-risk group, participants must meet criteria for a prodromal syndrome based upon the Structure Interview for Prodromal Syndromes (SIPS) interview. Inclusion criteria for the HC group is as follows: a) age 16-24, b) no diagnosable psychotic disorder, c) no history of substance use disorder within 6 months of the screening interview, d) no history of head injury, tic disorder, neurological disorder. Substance use will be assessed during the prescreener, and the participants who consent to the study will be asked to provide a urine sample for drug testing (see Procedures Involved). Exclusions criteria for all subjects include: a) less than 16 or greater than 24 years of age, people who are claustrophobic (people who have a fear of being in a closed space), b) have a history of significant head injury: This will be based off of the Childhood Brain Injury Scale to determine, if a head injury occurred, whether consciousness loss of consciousness. If consciousness was lost between 2-30 minutes, and/or post-traumatic amnesia/confusion <1 hour and/or other symptoms (cognitive or behavior changes) lasting 1-24 hours, participants are not eligible to participate in the study (First, 2010), c) other neurological disorders that could affect brain functioning such as Multiple Sclerosis, Stroke, Tumors, Epilepsy, Alzheimer's disease, Parkinson's disease, d) mental retardation, e) history of substance use disorder within 6 months of screening interview, f) have a psychotic disorder, taking antipsychotic medication, and/or have exhibited serious self-harm behaviors, g) pregnant females (see scanner protection description below), h) people who have contraindications to magnetic resonance (MR) scanning including intracranial, intraoribital, or intraspinal metal, pacemakers, cochlear implants or other non-MR-compatible devices, face or neck tattoos, and i) inability of the subject or their parent/guardian to understand the informed consent document (see below), j) inability of the subject or parent/guardian to understand written or spoken English. For the at-risk group, participants meeting criteria for an Axis I psychotic disorder will be excluded (e.g., schizophrenia, schizoaffective disorder, psychosis NOS, brief psychotic disorder, mood disorder with psychotic features). Medications are not a basis for exclusion because of the sensitive nature of this research except for antipsychotics. Similar studies have adopted a general policy allowing any outside treatment to remain because of ethical concerns that may arise. During analyses, medications (individuals taking antipsychotics will be excluded. All other medications are accepted) will be treated as covariates such as antidepressants and stimulants. Although this may limit statistical power, the exploratory nature of this study allows for such. In Dr. Mittal's current protocol, only 8% of prodromal participants are using medications, such as antipsychotics. Consistent with past exercise studies, all participants will be sedentary (i.e., no more than 60 minutes of maximal heart output per week for at least the past six months). This will not be the same as targeted treatment interventions at a high intensity and frequency of 2-3 times a week for 65% or 85% of VO2max for 60-90 minutes. Qualitative substance use will be evaluated by urine drug screening; urine drug screens which best document recent ingestion (which may have precipitated a worsening of symptoms).

For the scan portion of the study, in order to protect the health and safety of the participants, exclusion criteria for this study will include any contraindication to magnetic resonance scanning

(e.g., metal in body, claustrophobia, pregnant). These exclusions are specific to MRI and are consistent with most studies involving MRI. Potential participants will be screened for the presence of any of these exclusion criteria prior to participating in this MRI study. Participants will be asked to complete the CTI required safety form prior to their scan.

We will also exclude adults unable to consent, pregnant women (due to the scanning requirements), and prisoners because these populations are not relevant to our present research. We will be including individuals that are not yet adults (16-18 years of age). Specific procedures for these populations are described throughout this protocol.

Study Timelines
Participants will be enrolled in the study for two years. We will be doing 12 and 24 month follow ups so we do not expect this study to be complete until July 2021. We have made the 12 month follow up available to do on Zoom with an optional additional consent/assent form.

Procedures Involved
Overview
Over a 2-year period, we hope to recruit 36 UHR youth (to yield 30 because of an expected 20% attenuation: 15 in the exercise and 15 in the waitlisted-control). Participants will first attend a screening session that will be roughly 1.5 hours (please see Table 1 below) and if they meet criteria for UHR, they will be invited to join.

Then, participants will return for a longer assessment that will examine diagnosis (Table 2), cognition (Table 2), brain volume (Table 2), and cardiovascular fitness (Table 3). This baseline assessment can be completed in one visit but also broken into several short visits if the participant wishes. The screening, diagnosis, and cognitive assessment will take place in the ADAPT lab at 1801 Maple Avenue in Evanston, IL and the cardio fitness will take place in the Northwestern University Department of Physical Therapy and Human Movement Science located at 645 N. Michigan Avenue, 10th floor, Chicago IL 60611. **In the table, we have referred to this as "Downtown"** (this fitness portion takes 30 minutes pre and post exercise intervention and will be monitored by an exercise physiologist).

After the baseline assessment, participants will be randomized into the following two conditions: exercise or waitlist control. The 15 UHR exercise group participants will be involved in a 3-month exercise treatment 2x a week at moderate-vigorous levels. This will take place in the Evanston ADAPT lab and will be monitored by an exercise physiologist (Elizabeth Skender). For participants who are unable to come to Evanston twice a week, we will offer the downtown location as an alternative for one or both weekly exercise sessions.

In total, this will result in 24 visits (each visit is 40 mintes). After, the 12 weeks are completed, participants will come back and simply repeat the baseline visit again (with the exception of the screening) (note: this is termed the post-exercise follow-up visit). This will be a total of 5 hours, and can be broken down into shorter visits based on the individual needs of a participant.

Finally, after the post-exercise period, participants will be invited back at 1 year and 2 years later for a clinical assessment (this will include a 3 hour battery repeating the symptom and diagnostic measures that were noted at baseline).

For the 15-waitlist control participants, the procedures are the same however they will NOT be undergoing the exercise intervention. They will simply be asked to come back after 3 months to do all post intervention assessments. These participants will also be invited back 12 months and 24 months later for follow up. The 12 month follow up interview will be optionally offered on Zoom secure video conferencing for CHR participants. The rationale is that the clinical group is the research priority during the remote work period before the return to Northwestern's campus and the control group will be invited to follow up interviews normally in person at that time.

The healthy control (HC) participants will only be invited to baseline, 12-month, and 24-month visits. We will not be inviting the HC group for the 3-month follow up because we do not anticipate any diagnostic or brain structure changes in this population. All procedures will be the same except for the cognitive battery (they will not complete MATRICS and RISE because these would not be a valid assessment of cognitive function in HC population) and the exercise assessment (because we are not looking at a 3-month change in HC group, they will not complete the VO2max). In addition, HC group will complete both fMRI tasks during the baseline visits.

Below is a walk through of all visits:

Table 1: Screening Visit

Visit (1 visit)	Time	Location	Time Point
1. Screening 1a. SIPS Positive	1.5 hours	ADAPT Lab	Screening

Table 2: Pre-Intervention (Both UHR groups)

Visit (1-3 visits)*	Time	Location	Time Point
2. Clinical Assessment: 2a. Cortisol Sampling-4 saliva samples and a hair sample 2b. Optional Blood Sampling and a Health Behaviors Questionnaire and a Symptom Checklist 2c. Food and Activity Log 2d. Child Hood Brain Injury Scale 2e. Drug and Alcohol Use Scale 2f. Hospitalizations 2g. Psychosocial Therapy 2h. Medication Log	1.5 hours	ADAPT Lab	Pre-Intervention

2i. Global Role/Social functioning 2j. SIPS (negative, disorganized, general) 2k. SCID 2l. PINS 2m. Exercise Survey 2n. Calgary Depression Scale 2o. Beck Anxiety Scale 2p. Beck Depression Inventory 2q. 6 take home samples will be given 2r. WRAT			
3. Cognitive Battery: 3a. MATRICS 3b. RISE Task 3c. Urine Sample	2 hour	ADAPT Lab	Pre-Intervention
4. Scan 4a. Structural Scan 4b. fMRI Scan and MID task	1.5 hours	CTI	Pre-Intervention
5. Initial Exercise Assessment	45 minutes	Downtown	Pre-Intervention

Table 3: HC baseline visits

Visit (1-3 visits)*	Time	Location	Time Point
2. Clinical Assessment: 2a. Cortisol Sampling-4 saliva samples and a hair sample 2b. Optional Blood Sampling and a Health Behaviors Questionnaire and a Symptom Checklist 2c. Food and Activity Log 2d. Child Hood Brain Injury Scale 2e. Drug and Alcohol Use Scale 2f. Hospitalizations 2g. Psychosocial Therapy 2h. Medication Log 2i. Global Role/Social functioning 2j. SIPS (negative, disorganized, general) 2k. SCID 2l. PINS 2m. Exercise Survey	1.5 hours	ADAPT Lab	Baseline

2n. Calgary Depression Scale 2o. Beck Anxiety Scale 2p. Beck Depression Inventory 2q. 6 take home samples will be given 2r. WRAT 2s. Urine sample			
4. Scan 4a. Structural Scan 4b. fMRI Scan and MID task 4c. SOT task	*2 hours or 2 visits: 1.5 hours and 30 minutes	CTI	Baseline

*depending on participant needs and preferences

Table 4: Exercise Intervention (ONLY FOR THE 15 UHR exercise group)

Visit (24 visits)	Time	Location	Time Point
6. Exercise Intervention (including the Orientation Tour and Affective Response Scales) PANAS and UFOV (will be given before and after exercise session 1, week 5 sometime, week 9 sometime, and week 12 sometime)	2x per week for 12 weeks (40 minutes each session)	Adapt Lab Or Downtown	Intervention

Table 5: Post Intervention (Both UHR groups)

Visit (1-3 visits)*	Time	Location	Time Point
7. Clinical Assessment: 7a. Cortisol Sampling-4 saliva samples and a hair sample 7b. Optional Blood Sampling and a Health Behaviors Questionnaire and a Symptom Checklist 7c. Food and Activity Log 7d. Child Hood Brain Injury Scale 7e. Drug and Alcohol Use Scale 7f. Hospitalizations 7g. Psychosocial Therapy	1.5 hours	ADAPT Lab	Post-Intervention

7h. Medication Log 7i. Global Role/Social Functioning 7j. SIPS (negative, disorganized, general) 7k. SCID 2l. PINS 7m. Exercise Survey 7n. Calgary Depression Scale 7o. Beck Anxiety Scale 7p. Beck Depression Inventory 7q. 4 take home samples will be given 7r. WRAT			
8. Cognitive Battery: 8a. MATRICS 8b. RISE Task 8c. Urine Sample	2 hour	ADAPT Lab	Post-Intervention
9. Scan 9a. Structural Scan 9b. fMRI Scan and SOT task	1.5 hour	CTI	Post-Intervention
10. Post Exercise Assessment and Feedback Session	45 minutes	Downtown	Post-Intervention

*depending on participant needs and preferences

Table 6: 12-month and 24-month Visits (All three groups)

Visit (1 visit)	Time	Location	Time Point
2. Clinical Assessment: 2a. Cortisol Sampling-4 saliva samples and a hair sample 2b. Food and Activity Log 2c. Child Hood Brain Injury Scale 2d. Drug and Alcohol Use Scale 2e. Hospitalizations 2f. Psychosocial Therapy 2g. Medication Log 2h. Global Role/Social Functioning 2i. SIPS (positive, negative, disorganized, general) 2j. SCID 2k. PINS 2l. Exercise Survey	3 hours	ADAPT Lab Or Over the phone/Zoom	12-month 24-month

2m. Calgary Depression Scale 2n. Beck Anxiety Scale 2o.4 take home samples will be given			

NOTE: Visits can be completed in 1-3 visits depending on what participants prefer.

COVID-19 Symptom Checklist & Procedures

If participating in person for any portion of the study, participants will be required to complete a COVID-19 pre-screening checklist within 24 hours before the appointment. This checklist will be sent via email to the participant upon confirmation of their in-person appointment. The form is brief and does not ask for vaccination status. If the individual answers "Yes" to any of the screening questions, the study team will cancel the study visit. If the individual is experiencing any of the above symptoms, study team members will recommend that they contact a doctor to determine if seeking medical care or being tested for COVID-19 is necessary. The study team member coordinating the visit will attempt to reschedule the session for a date at least 14 days later. However, the potential participant must pass pre-screening before proceeding with the in-person study visit. COVID-19 prescreening checklists will be stored on Box SAFER, separate from study data.

Participants will be asked to wear a mask for the duration of all study components in which the participant will be in the same room as research study team members. This is a requirement that will be included in the consent forms for all participants, and they will be informed that refusal to wear a mask or failure to comply can result in being removed from the study before it is completed.

Design of the Proposed Study

1. Screening Visit
Participants will first attend a screening session (roughly 1.5 hours) and if they meet UHR criteria discussed throughout the protocol and in consent forms, they will be invited to join the study (note: we propose to screen 54 people to identify the 36 eligible UHR individuals). HC participants will be screened using the same measures to rule out UHR criteria. If potential HC participants present with the prodromal syndrome based on the SIPS scores, they will be informed that they cannot participate in the HC groups and provided with referrals to community mental health providers based on their specific needs. If they are still interested in participating in the study, they will be given an option to screen for the URH groups. At that point, we will follow the protocol outlined for UHR groups.

2. Clinical Assessment

Background information will be obtained at the beginning of the clinical evaluation. This will allow us to understand what the patient's history is like in order to fully understand their current experiences. This background packet will include questions about brain injury from the Childhood Brain Injury Scale, drugs and alcohol from the Drug and Alcohol Scale, hospitalizations from the Hospitalizations Questionnaire, therapy from the Psychosocial Therapy Questionnaire and medications from the Medication Log. This will be given at baseline, 12 month, and 24 month visits.

The Structured Interview for Prodromal Symptoms (SIPS) (Miller et al., 1999) will be administered to initially detect the presence of a prodromal syndrome at the screening interview (the presence of a prodromal syndrome is necessary for inclusion in the at-risk group), and then to formally assess attenuated negative and disorganized symptoms after inclusion in the study. It will also be administered post-trial to track changes in clinical symptoms post intervention trial. The SIPS contains an instrument, the Scale of Prodromal Symptoms (SOPS), which rates the severity of relevant dimensions including positive, negative, and disorganized symptoms along a 7-point scale ranging from absent to severe and psychotic. Prodromal or high-risk syndrome will defined by moderate levels of positive symptoms and/or a decline in global functioning accompanying the presence of schizotypal personality disorder and/or a family history of schizophrenia. The Structured Clinical Interview for DSM-IV (SCID-I) will be used to determine the presence of Axis I psychotic disorders (for rule-out) and to classify diagnostic status for non-psychotic axis-I disorders (First et al., 1995). It will also be administered post-trial to determine any changes in clinical status. Each of the measures has been used with psychotic subjects and demonstrated reliability with adolescent populations (Martin et al., 2000, Miller et al., 2003a, Mittal et al., 2008b, Howes et al., 2009, Mittal et al., 2010c). Advanced doctoral students and clinical psychologists will conduct the interviews. As part of the ongoing ADAPT clinic, all interviewers in our program will participate in an in-depth training program regarding the administration and scoring of the SIPS and SCID and will be required to independently rate a minimum of six SIPS and SCID training videos, followed by four live supervised assessments (by the PI Mittal). Interviewers will be required to achieve sensitivity and specificity Kappas of at least .80 regarding SIPS and SCID symptoms, as well as 90 percent agreement on all diagnostic classifications across assessments. Following this stage, ADAPT examiners will continue the training, observing and providing ratings of live interviews with high-risk adolescents specifically. ADAPT raters have been observed while conducting ratings on live interviews with high-risk adolescents; intraclass correlations (ICCS) over .80 for all symptom ratings and kappa of $\geq .80$ for prodromal syndrome diagnoses will be met for each interviewer prior to participation in formal interviews. In addition, Prodromal Inventory of Negative Symptoms (PINS) will be administered to assess five dimensions of negative symptoms: avolition, asociality, anhedonia, transitionary distress, and blunted affect/alogia. The interview is comprised if 23 items and includes probes for the interviewer which assess areas of functioning reflected by these domenstions. Each item is rated on a scale from 0 (absent) to 6 (extremely severe).

Role and social functioning will be assessed with the Global Functioning Scale: Role (GFS-R) (Niendam et al., 2006), and the Global Functioning Scale: Social (GFS-S) (Auther et al., 2006), which provide ratings on two separate 10-point Likert scales. On the GFS-R, a score of 10

indicates "Superior Role Functioning" (e.g., Independently maintains superior functioning in demanding roles), whereas a low score of 1 reflects "Extreme Role Dysfunction" (e.g., on disability, non-independent status). A score of 10 on the GFS-S reflects "Superior Social/Interpersonal Functioning" (frequently seeks out others and has multiple satisfying interpersonal relationships including close and casual friends), whereas the lowest score of 1 indicates "Extreme Social Isolation" (no social or family member contact at all). The scales were designed for adolescents and have been found valid and reliable in assessing prodromal populations (Cornblatt et al., 2007) and our group is familiar in working with these measures (Mittal & Walker, 2011a, Pelletier et al., 2013).

In addition, we may ask permission (participants to sign a release form) for us to speak to current therapists, psychiatrists, or other medical professionals involved in the mental health of participants. We ask to do this in order to fully understand the mental health history and background. We can better rate various scales, measures, and interviews with this knowledge. If participants choose not to give us permission to do so, they may still continue to participate in the study. This is considered additional material, but is not absolutely necessary. Detailed information regarding thoughts and experiences will be obtained during the clinical interview. Although information from current providers may provide useful supplementary information, this is not a requirement given the detailed structure of the interview. This has been the common and successful approach in our studies at the University of Colorado Boulder, and we will be extending this practice.

We will also ask participants to complete an exercise survey. This survey is a short self-report questionnaire designed to capture exercise and activity practices of adolescents and young adults. The Exercise Survey was designed by and Deighton and Addington (2013) specifically for examining exercise in UHR samples, and uses items applicable to the adolescent and young adult age range from widely employed measures of exercise and recreation practices such as the International Physical Activity Questionnaire: Short, The World Health Organization (WHO) Quality of Life-BREF, Motivations for Physical Activities Measure-Revised, and the Physical Self Description Questionnaire. The survey is brief but highly informative (asking about the frequency, intensity, and duration of recent exercise activity; See Appendix 2) and will be administered pre and post exercise intervention, as well as during the yearly longitudinal follow-up time points.

We will also assess symptoms of depression and anxiety using the self report measures named the Beck Anxiety Scale (Beck et al., 1998), Beck Depression Inventory (Beck et al., 1998), and the Calgary Depression Scale developed by Addington, Addington, and Schissel 1990, which is completed by the assessor based on interview. The scales will help supplement the questions given on the SCID noted above. This will be completed at pre and post exercise intervention, and 12 and 24 month visits.

We will ask participants to complete a puberty scale asking them to rate puberty milestones on a 4 point likert scale (not yet started, barely started, seems complete) or "I don't know".

Further, participants will be given a sheet with words listed on it ranging from simple to difficult. They will be asked to read the words and the assessor will keep track of incorrectly pronounced

words. This assessment called the Wide Range Achievement Test (WRAT) has been used in order to obtain a quick measure of general intelligence. Typically, general intelligence tests take several hours, and this is a quick and easy way to get this information.

Cortisol

Four saliva samples for cortisol assay will be collected in the ADAPT clinic at the pre and post exercise intervention, and at 12-month and 24-month assessment points. If participants choose to do the 12 and/or 24 month follow up over the phone, saliva sample tubes will be mailed to them to complete during the phone interview. A pre-labelled/prepaid package will be included for them to mail the completed samples back to ADAPT. Samples collected in the clinic will be collected at hourly intervals during the first morning of the initial and follow-up assessments while the diagnostic interviews and self-report measures are administered. Collection will begin around 9:30am, and subsequent samples will be obtained at hourly intervals, approximately 10:30, 11:30 and 12:30. A timer-alarm will be used to signal collection times. Participants will provide each sample in a plastic specimen tube prelabeled with participant's ID and sample number. Collection time is recorded on the label. Samples will be immediately stored at -20C in lab freezers, and kept frozen until assay. Because diet and activity affect cortisol, subjects will be given explicit instructions and provided a log to detail these activities. On the evening before saliva sampling, they will be asked to avoid alcohol and caffeine after 6:00 PM. On the morning of the assessment, they will refrain from exercise, caffeinated beverages, and consume only grains (e.g., toast, cereal, pastry), milk, juice or water. They will also avoid over-the-counter medications and physical exercise. Food, liquid, and medication consumption the previous evening and morning will be recorded (please see Food and Activity Log attached). For salivary cortisol assay, the Salimetrics (Salimetrics, LLC, College Park, Pa) High Sensitivity Salivary Cortisol Enzyme Immunoassay Kit will be used. This assay captures the full range of salivary cortisol levels (0.003 to 3.0µg/dL) requiring only 25 uL of saliva per test. A built-in pH indicator detects acidic or basic samples.

In addition to collecting salivary cortisol during pre and post exercise intervention, 12-month, and 24-month assessments, the participants will be asked to take home four plastic specimen tubes pre and post exercise intervention, 12-month and 24-month assessments. They will be given these tubes at the end of the clinical assessment (Please refer to tables 2, 4, and 5). These samples will be used to measure the Cortisol Awakening Response (CAR). The CAR is a new area of research that provides a good measure of HPA integrity (Wilhelm, Born, Kudielka, Schlotz, & Wüst, 2007). The participant will be instructed to give a saliva sample on any day prior to coming back for their next visit. Instructions on when to provide the samples will be given (see attached document, "Cortisol Sample Instructions"). There is a section in the Sleep and Activity log for the participant to record the time and day that these samples are given as well as serve as a reminder to provide the samples. The participant is instructed to provide the samples immediately after waking, 30 minutes after awakening, 45 minutes after awakening, and immediately before going to sleep. The tubes will be labeled with their participant ID followed by a 01, 02, 03, 04 to denote the succession of samples. The participant will be instructed to bring the samples back to the ADAPT office. Upon return to ADAPT, specimens will be stored in a freezer until ready for assay along with the other samples taken during the assessment. Please note that we do not request participants to store cortisol samples in a freezer when they take them home. If participants choose to do the 12 and/or 24 month follow up over the phone,

the take home saliva sample tubes will be mailed to participants to complete after the phone interview at the times noted above. A pre-labelled/prepaid package will be included for them to mail the completed samples back to ADAPT.

In addition to saliva samples, participants will be asked to provide a hair sample for cortisol analysis. The assessor or lab manager will collect a hair sample from the participant. They will cut a small strand of hair from the crown of the participant's head. They will also be asked the following questions:

1) How frequently do you wash your hair? (times/week)
2) Do you use a conditioner? (yes/no)
3) Do you bleach your hair? (yes/no)
4) Have you recently had a perm? (yes/no)
5) Do you use hair straighteners? (yes/no)

The strand of hair will be taped to a piece of foil and placed in a confidential, locked, cabinet.

Blood Draw, RNA Extraction and BDNF and Inflammation Analysis:

Before the blood draw, participants will be asked to complete a questionnaire asking about health behaviors (alcohol consumption, smoking, medication use, recreational activities, and reproductive health for female participants), a questionnaire about symptoms (e.g., headache, dizziness, chest pain), and questions about chronic illnesses and respiratory illnesses in the last two weeks. These questions are crucial for 1) data analysis because the blood sample can be affected by the health behaviors outlined above and 2) determining whether blood can be drawn on the scheduled day. If the participant had a respiratory illness (e.g., cold, flu) in the last two weeks, the blood draw will be rescheduled because the cell count would likely be impacted by the illness.
In addition, if the participant agrees to the blood draw, the trained phlebotomist will take participants' body measurements: weight, height, waist, and hip. These measures need to be factored in during the data analysis because they are related to inflammatory markers. Research suggests that BMI, waist circumference, and waist to hip ration are all associated with IL-6, TNF- α and CRP (O'Connor et al., 2009). During that procedure, the phlebotomist will ensure the participants' privacy is protected by minimizing physical contact (having the participant hold the measurement tape during hip and waist measurement, keeping appropriate distance) and talking the participants though the steps. The participants will also be informed they may tell the phlebotomist if they are uncomfortable with the procedure and that they can stop at any point without penalty.

Blood sampling will be optional, and the participant's decision not to consent to the blood draw will not affect participation in any of the other procedures. For those participants who consent to the blood draw, less than 30 mL of blood will be taken via antecubital blood draw by a trained phlebotomist. Collected into 2 PAXGene tubes, stored (frozen at -80 degree Celcius) and shipped to Drs. Hutchison and Bryan at the University of Colorado Boulder. There, blood will be collected into a 4 mL Vacutainer tube containing EDTA. A cell counter (Beckman Coulter 5-part Hematology Analyzer) will be used to quantify the presence of different cell populations in whole blood, to determine whether gene expression values differ depending on blood cell composition. The mRNA will be extracted from blood samples using the Qiagen RNAeasy kit

and BDNF mRNA will be assayed using real time PCR and a commercially available assay from Applied Biosystems.EndFragment. Blood samples will be collected pre and post exercise intervention for the UHR Exercise group and pre and post waiting period for the UHR waitlist control.
A sample of venous blood will be taken at the same time into a Vacutainer Serum Separation Tube (BD Biosciences), which is then centrifuged at 1200 rpm for 10 minutes (in the ADAPT lab Centrifuge). Samples will then be aliquoted into microfuge tubes and frozen at -80 degree Celsius until processing. These analyses will focus on inflammatory markers associated with exercising. Another sample will be processed at Dr. Gregory Miller and Dr. Edith Chen's lab located at the same location as the ADAPT lab. Only trained and authorized lab members will be responsible for transporting the blood specimens for processing. During this process, blood will be collected into a 4 mL Vacutainer tube containing EDTA. A cell counter (Beckman Coulter 5-part Hematology Analyzer) will be used to quantify the presence of different cell populations in whole blood, to determine whether gene expression values differ depending on blood cell composition.
The total amount of blood drawn at each time point is less than 30mL between 4 tubes.

Urine samples:
We will ask participants to urinate in an icup. Icup is a brand of drug testing cups. If the results (which show up immediately) indicate that the participant is under the influence, they will be asked to reschedule their visit when they are not under the influence. With this information, we will include an appropriate referral.

Audio and/or Video Recordings
We will videotape the clinical interviews portion of the study. On the consent form, we included information about the video taping process, and whether or not participants agree to this. Participants will be informed that this is for educational purposes and this allows us to make sure we are doing everything correctly. Participants will be also informed that videotapes may be used for coding various portions of the study such as examining emotions. Additionally, this will allow us to have accurate consultation from the consultants involved. If participants decide not to be videotaped, they still may participate in the study.
Video tapes will be deleted upon participants' request, although the participant will not be permitted to review the tape before doing so. Videotapes will be retained for research and/or training purposes for 30 years after which time they will be destroyed unless participant provide written permission for their continued use. In the future, the videotapes may be used for coding various components of the study (if consent is obtained).

Participants who do not consent to be videotaped will not be videotaped. Participants who consent to be videotaped and then withdraw from the study or are ineligible will have their videotapes erased/deleted.

3. Cognitive Battery
The battery is designed to assess spatial memory, verbal learning, and episodic memory as well as broad cognitive function. This will include the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (Green & Nuechterlein, 2004) which provides scores for domains of processing speed, attention/vigilance,

working memory, verbal learning, visual learning, problem solving, social cognition and an overall composite score. The MATRICS includes the Brief Assessment of Cognition in Schizophrenia (BACS), Symbol-Coding (Timed paper-and-pencil test in which respondent uses a key to write digits that correspond to nonsense symbols), Category Fluency: Animal Naming (Oral test in which respondent names as many animals as she/he can in 1 minute), Trail Making Test: Part A (Timed paper-and-pencil test in which respondent draws a line to connect consecutively numbered circles placed irregularly on a sheet of paper), Continuous Performance Test—Identical Pairs (CPT-IP) (Computer-administered measure of sustained attention in which respondent presses a response button to consecutive matching numbers), Wechsler Memory Scale®—3rd Ed. (WMS®-III): Spatial Span (Using a board on which 10 cubes are irregularly spaced, respondent taps cubes in same (or reverse) sequence as test administrator), Letter-Number Span (Orally administered test in which respondent mentally reorders strings of number and letters and repeats them to administrator), Hopkins Verbal Learning Test—Revised™ (HVLT-R™) (Orally administered test in which a list of 1 words from three taxonomic categories is presented and the respondent is asked to recall as many as possible after each of three learning trials), Brief Visuospatial Memory Test—Revised (BVMT-R™) (A test that involves reproducing six geometric figures from memory), Neuropsychological Assessment Battery® (NAB®): Mazes (Seven timed paper-and-pencil mazes of increasing difficulty that measure foresight and planning), and the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT™): Managing Emotions (Paper-and-pencil multiple-choice test that assesses how people manage their emotions). This collective battery has been specifically designed, and validated for administration to psychosis spectrum individuals and is designed to take 60-90 minutes to complete.

Episodic memory is a critical cognitive process affected in the psychosis spectrum (Eastvold et al., 2007), and tied with aerobic fitness in other populations (Bunce & Murden, 2006). Many of the common paradigms used to assess relational encoding and retrieval allow for the nature of the encoding strategy to be up to the participant, leaving open the possibility that poor task performance simply reflects a failure to apply relational processing, rather than a fundamental deficit in the ability to engage in such processing. In addition to the MATRICS consensus battery participants will also be administered the behavioral version of the Relational and Item Specific Encoding and Retrieval (RISE) task, which has been determined to gauge hippocampal mediated episodic memory function while explicitly controlling whether participants engage in item-specific or relational memory processing (Ragland et al., 2012). The task is part of the final selection of CNTRICS initiative, and demonstrates excellent test-characteristics (Gold et al., 2012). Stimuli consist of visual object representations of word stimuli (selected from a standardized corpus of photographic images; http://cvcl.mit.edu/MM/). The RISE assessment includes several components and is administered with E-Prime® (version 2.0). For the Item-Specific encoding component, a total of 36 stimuli are presented for two seconds each, with a one second inter-stimulus-interval (ISI), and subjects make a two-button "yes/no" response to indicate whether the objects are "living" (this level-of-processing manipulation controls for potential group differences in strategy generation). For the Relational Encoding component 18 pairs of visual objects are presented for 4 seconds each, with one second ISI and subjects make a two-button "yes/no" response to indicate whether one item could fit inside the other item. After the encoding conditions, two retrieval tasks are administered. For the Item Recognition component, all 72 objects studied during the encoding trials (36 item-specific and 36 relational

targets) are randomly intermixed and presented with 72 new unstudied foils, and participants indicate whether each test item was "old" (left hand response) or "new" (right hand response) and rate their confidence using one of three buttons (i.e., 3 = high, 2 = medium, 1 = low). Finally, the Associative Recognition component includes the 18 original objects pairs studied during the relational encoding, which are then randomly intermixed and presented with 18 rearranged object pairs consisting of items presented during different encoding trials an not originally paired together. Subjects make a two-button "yes/no" response to indicate whether items in each pair had been presented "together." To prevent additional encoding of the relational object pairs the item recognition task precedes the associated recognition task. The familiarity and recollection performance as well as hit rates and false alarm rates following encoding reflect the cognitive and neural mechanism underlying relational encoding and retrieval. The complete procedure, including practice, encoding, and retrieval required 20 minutes to complete. In addition to being highly innovative and amendable to administration in psychosis spectrum populations (the task uses visual objects rather than words to improve patient understanding of encoding instructions; because individuals with psychosis have prominent task-switching difficulties, encoding conditions are alternated in a pseudo-random block design rather than in the fully randomized design; participants are presented with 3 second instruction screens to remind them of the encoding condition between blocks), the task specifically targets an NIMH prioritized construct as well (http://www.nimh.nih.gov/research-funding/rdoc/rdoc-constructs.shtml#active_maintenance). Psychology Masters and Ph.D. level students will administer the entire battery under the supervision of Dr. Mittal. Taken together, this battery was kept brief to limit any potential participant strain over the multiple testing periods.

We will also be measuring acute stress. We will do this using the the Positive and Negative Affect Scale (PANAS), which is a paper and pencil 20-item self-report questionnaire administered to the patients to assess their current mood state (Watson et al., 1988). The questionnaire takes approximately five minutes and will be repeated once monthly before and after exercise for the duration of the study. Additionally, we will use the Useful Field of View (UFOV), which is a computerized measure of selective attention and visual processing speed. Subjects will be asked to identify a central stimulus, as well as locate a peripheral target among distractors on the computer. Testing will last approximately five minutes and will be repeated once monthly before and after exercise for the duration of the study. Specifically, they will both be given before and after exercise session 1, week 5 sometime, week 9 sometime, and week 12 sometime)

4. Exercise Intervention

VO_{2max} Graded Treadmill Test: Participants will be asked to meet in downtown Chicago at the Northwestern University, Department of Physical Therapy and Human Movement Science, 645 N. Michigan Ave. 10th Floor, 60611 for the initial exercise assessment pre and post exercise intervention. Prior to the initial exercise assessment, participants will be given information verbally on how to prepare for this test over the phone or during their last visit at ADAPT. We will inform participants to wear exercise clothes (comfortable clothing, tennis shoes, sports bra for women), bring water and water will also be provided if necessary, eat only very light meals before coming in for the assessments, and refrain from ingestion of caffeinated substances for at least 2 hours prior to the session

Once at the VO_{2max} center, a trained exercise physiologist (Elizabeth Skender) will conduct the maximal exercise test. First, a resting 12-lead ECG will be recorded in the recumbent and upright positions immediately prior to the exercise test, as well as during the test. If the findings on the resting ECG do not contraindicate exercise, the exercise test will be performed. Contraindicators include the following: (a) ST-segment depression of more than 0.2 mV that is either horizontal, downsloping, or slowly upsloping (less than 1 mV/sec) and lasts for 0.08 sec, or ST-segment elevation greater than 0.1 mV; (b) chest pain or discomfort; (c) serious arrhythmias, including multifocal PVCs, ventricular tachycardia, frequent (>10/min) PVCs or couplets, or sustained atrial tachyarrhythmias; (d) A-V block or other conduction defects; (e) a fall of systolic blood pressure of 10 mmHg or greater from the peak level with increasing exercise intensity; (f) diastolic blood pressure above 110 mmHg or systolic above 220 mmHg; (g) dizziness; (h) ataxic gait; and (i) pallor or cyanosis. Elizabeth Skender, who is The American College of Sports Medicine certified exercise physiologist and has a successful completion of an American Heart Association-sponsored course in advanced cardiac life support, is qualified to conduct and monitor the ECG procedure. In addition, she has knowledge of appropriate indications and contraindications for exercise testing, competence in cardiopulmonary resuscitation, knowledge of cardiac arrhythmia and the ability to recognize and treat various arrhythmias, and knowledge of endpoints of exercise testing and indications to terminate exercise testing. As a part of her ACSM certification, she also qualified to take blood pressure and measure ratings of perceived exertion (RPE).

Maximal aerobic power (VO2max) will be measured by indirect calorimetry (TruMax 2400, ParvoMedics, Sandy, UT) during the GXT. A warm-up period on the treadmill will be used to identify the walking speed that generates a HR that is 65-70% of the age- predicted HRmax. The speed of the treadmill will remain the same throughout the test but the incline of the treadmill belt will increase 2% every 2 min (or 2.5% for speeds 6 mph or greater). The ECG will continuously monitor the subject's HR throughout the entire VO2 max test. Blood pressure will be taken every minute of the test, and the subject's RPE will be recorded at each minute. The treadmill speed is determined using participant's heart rate and RPE and can vary greatly between subjects (1.5-10+ mph). Because all participants will be sedentary, a speed that elicits 70% of age-predicted max heart rate and an RPE rating of around 13 ("somewhat hard") will be used to begin the test. Staying within these parameters generally yields an 8-12 min test; the recommended target for VO_{2max} testing (Hollenberg et al., 1998). The determination of when a participant has reached VO_{2max} is not without controversy, (Magnan, 2013) and will ultimately be up to the participant, who chooses when they can no longer continue. This study will determine a valid VO_{2max} using both the primary criterion of having achieved a plateau in VO_2 as well as secondary criteria outlined by Pimentel and colleagues (Pimentel et al., 2003) including respiratory exchange ratio (RER)max≥1.1, RPEmax≥18, and age predicted heart rate max ±10bpm. VO_{2max} will be used as a baseline measure of cardiovascular fitness and will serve as the basis for exercise prescriptions. There is ample evidence in the literature that VO_{2max} is an appropriate measure for youth in this age range (Pheiffer et al., 2008). Additional measures of cardiovascular fitness obtained in the course of the assessment include ventilatory threshold (VT) (Ekkekakis et al., 2008) and VO_2 peak (Cooper et al., 1984), both of which are related but distinct measures of cardiovascular fitness and have been used successfully in studies of adolescents and young adults. These variables will then serve as objective outcome measures to

determine whether participation in one of the aerobic exercise (moderate versus vigorous intensity) led to an increase in cardiovascular fitness.

Exercise Intervention at Northwestern University in Evanston, IL

Orientation Tour
During the orientation tour, we will show participants the facility, share their exercise prescriptions with them, and work with them and their families to organize transportation for the sessions. We will also provide participants with more information about the incentives for participation and discuss factors relating to how to best keep them motivated. This will also be a great time for participants to meet the exercise staff (including an expert exercise physiologist) that will work with them to help meet aerobic fitness goals. This portion of the study will be apart from the exercise intervention. During the orientation tour, they will receive incentive flyers, exercise is fun flyer, and payment information forms (please see supporting documents).

The exercise intervention will be tailored to each person's current exercise fitness level. We will use 80% of VO_{2max} and ask participants to exercise 2 times a week. The first 10 minutes of the visit will include warming up. Next, participants will be asked to run for 30 minutes. Every 10 minutes they will be asked to run at a slightly higher intensity (a faster jog) for 3 1-minute intervals to get to 95% of VO_2max. The purpose of adding brief sessions of high intensity interval training (HIIT) to participants' exercise prescription is to increase rates of their fitness improvement. Recent studies suggest that HIIT is associated with higher improvements in adolescent and young adult aerobic fitness than more traditional continuous endurance training (Buchan, et al., 2012, Costigan et al., 2015, Logan et al., 2014, Matsuo, et al., 2014). Risks associated with brief spouts of HIIT are no greater than risks associated with aerobic exercise described in the Risks to subject portion of the protocol. In addition, individuals that are enrolled in the study will be asked not to partake in any physical activity outside of the exercise intervention. Based on our pilot data, which suggest that prodromal participants do not engage in physical activity but instead have more sedentary lifestyles, we do not think that excess physical activity will be a concern. Later in a different phase (which will be included in a separate application), the controls will be assessed for fitness before and after the exercise intervention and any increases in fitness will be considered outside physical activity. Increases in fitness will be treated as covariates.

Most (if not all) exercise sessions will be monitored by the exercise physiologist. In an event the exercise physiologist is not available for the scheduled session, the research coordinator may step in to monitor the session to ensure participants are staying on the 2 session per week schedule. According to ACSM Guidelines for Exercise Testing and Prescription, 9th edition, "The health/fitness and clinical exercise professional may determine the level of supervision that is optimal for an individual by evaluating information derived from the pre-exercise evaluation as indicated by the individual's exercise goals and health status" (the VO2max test in our case). "Supervision by an experienced exercise leader can enhance adherence to exercise and may improve safety for individuals with chronic disease and health conditions". We are recruiting only low risk participants who do not have chronic diseases or health conditions that would put them at high risk for a detrimental event during exercise. Therefore, the supervision is not necessary (i.e., healthy adolescents and young adults could to the prescribed exercise regimen on

their own), and we monitor sessions to improve adherence, administer questionnaires, and to add a level of safety. However, we will be adding precautionary steps to ensure safety. Based off the VO2 max test and first few weeks of exercise sessions, the exercise physiologist will determine the level of supervision that is optimal for the individual. If for any reason the subject is severely deconditioned, or the exercise physiologist believes that they need an exercise professional's supervision, they will only be supervised by an exercise physiologist. However, if based on the VO2 max test and the subject's fitness level, the exercise physiologist determines that the research coordinator is an adequate level of supervision during certain exercise sessions, then that may be an option. Furthermore, we monitor heart rate and the perceived exertion every 5 minutes throughout the sessions.

Exercise Prescriptions. The initial exercise intensity will be 55% of VO_{2max}. This is the baseline fitness threshold for the study to see what their baseline fitness level is prior to intervention. Then, the intensity will be gradually increased to peak intensity over the first 3 weeks. The initial exercise duration will be 15 minutes, and duration will be gradually increased to 30 minutes over the first 3 weeks. Intensity will be constantly monitored during exercise using heart rate (HR) monitors. Once at full training intensity, the goal will be to maintain HR within ±5% of the target intensity. The primary mode of exercise will be treadmill walking/running or elliptical. Adding variety will keep participants engaged and interested, allowing us to better test feasibility of this study.

Feedback Session. At the end of the post exercise visits, participants will receive a feedback session with members that worked with them. This is an opportunity for participants to ask questions and receive appropriate recommendations and referrals, if needed. A feedback session is a great way to check in and get information regarding the participation. Additionally, it's a good way to wrap up the time in the lab and to remind the participant they will be asked to come in 12 and 24 months later. Additionally, participants will be given a take home packet consisting of a reminder of their next appointment and flyers. The first flyer will remind them about the opportunity to win incentives. The second flyer will be some information regarding the benefits of exercise, and other educational points. This allows participants to learn more about exercise throughout the process. Please see attached documents for more details.

Affective Response Scales (Hardy and Rejeski, 1989; Svebak and Murgatroyd, 1985; Borg, 1998): To check in with participants as they are exercising, we will be asking them questions about how they feel, how aroused they are, their thoughts, perceived exertion, and motivation. This will allow us to see how participants are able to handle the exercise intervention (contributing to the feasibility aims of the study).

5. Imaging Assessment and Analysis

PI Dr. Mittal and an experienced postdoctoral research assistant (PRA) will be responsible for preparing, analyzing, and interpreting the data. The entire imaging protocol including localizing images, gradient echo field mapping, arterial spin labeling scan, and BOLD weighted resting state scan takes approximately 30 minutes. Prior to scanning at each time point, each participant will be evaluated with a comprehensive screener detailed in the "Safety" section.

fMRI Monetary Incentive Delay (MID) Task. During the same session of the structural MRI scan, the participants will be asked to complete the MID task while undergoing an fMRI. They will complete 2 MID runs each lasting 9 minutes. On each trial, a cue will indicate whether participants can win money, lose money, or neither win nor lose money (neutral). Next they are instructed to press a response-box button as quickly as possible following the target stimulus. Finally, feedback will indicate whether participants won or lost that trial and whether or not they won/lost money for their response. Outcome probabilities are fixed by an adaptive algorithm by applying a sliding threshold that changes how quickly participants need to respond to receive win feedback. The algorithm tracks participants' response times and adjusts the response time window to keep the task difficulty consistent (at approximately 66% success rate). This means that if the participant is below 66%, the target duration is lengthened, and if the participant is above 66%, the target duration is shortened. There will be 150 trials and the total task takes about 20 minutes to finish. In win trials, participants win 20 cents, and in lose trials, they lose 20 cents. Participants can earn an average of $20 during this task ($0 lowest and $30 highest amount) which will be added to the total payment for this session. The participants will be made aware that the difficulty of the task is changing depending on their performance and that they are most likely to earn $20 during the task. This taks will be completed only at the baseline (pre-intervention).

fMRI Self Ordered Working memory task (SOT). Participants will complete a Self Ordered Working memory class in the scanner. Eight line drawings of difficult-to-verbalize objects will be presented, and participants will be instructed to select each object once, in any order. After each object is selected, all objects will be pseudorandomly rearranged on the screen. Participants will then select an object not already selected so that at each step there is one more previously selected object to remember. A perceptual and motor control task will be used following identical procedures except that one object will be marked with an asterisk, and participants will be instructed to select the marked object, as a control condition. Participants will be paid $0.25 per correct response for both tasks. The primary measure of performance will be working memory capacity. Participants are able to earn between $0.25 (one trial correct) and $36 (144 trials correct) for an average of approximately $20. This task will only be completed at the 3 month follow up (post-intervention).

MRI Post Processing

PI Dr. Mittal holds significant experience in utilizing structural imaging to understand grey matter changes both in early psychosis and neurodegenerative disease and will be responsible for preparing the images for analysis (registration and delineation) and analyzing the data and interpreting results. Medial temporal structures (hippocampus and parahippocampal gyrus) will be delineated automatically on MRI using the FMRIB's Integrated Registration and Segmentation Tool (FIRST) algorithm within the FMRIB's Software Library (FSL) image-processing suite (Patenaude, 2007). Researchers have found close correspondences between FIRST and manually derived volume values (de Jong et al., 2008). Dr. Mittal has also utilized this program in other recent studies of high-risk patients (e.g., Mittal et al., 2010a). To employ FIRST, each subject's whole-brain IR-FSPGR will be converted from DICOM to Analyze format and cropped below the head. The resulting volume will be resliced to an axial-oblique orientation aligned with the AC-PC plane. It will then be transformed into MNI152 space before being loaded into FIRST. FIRST was developed by the FMRIB Centre in the Department of

Clinical Neurology at Oxford and represents a cutting-edge addition to the widely used FSL medical image-processing package, incorporating several major advances in brain voluming of the last decade. Briefly, the individual subject's brain MRI is compared to a large database of standard brains maintained by Harvard/MGH. These brains have been carefully parcellated into numerous volumes-of-interest (VOIs), each representing a different brain anatomic structure, by hand. A surface mesh is then applied to each candidate VOI in the subject's brain, (i.e., the actual surface is approximated by a very complicated contiguous net of a large number of tiny polygons (e.g., triangles) each with vertices (mesh points) and an interior area (facet)). The shape formed by the points mesh is then described quantitatively as a 3D distribution in space, composed of varying amounts of a set of standard deformable distributions. The T1 MRI intensity at each facet of the mesh surface is normalized to correct for instrumental and other inter-subject differences in intensity. A separate 3D distribution is then derived for the intensity. A "training set" of standard VOIs is extracted from the database. Iterative curve fitting is then applied until a linear combination of the standard VOIs is found that best reproduces the shape and intensity distributions of the subject's VOI. That yields the final volume. FIRST also returns values for each participant's total intracranial volume (TICV; the sum of whole-brain grey matter plus white matter plus cerebrospinal fluid) and each structure is then divided by the TICV to control for whole brain volume. To confirm volumes derived using FIRST, results for each subject will be also checked by visual inspection by Dr. Mittal an experienced PRA. Secondly, the structures will be evaluated with vertex analyses (assessing changes in shape post trial on a per-vertex basis), which will also be carried out utilizing FIRST (first_utils). Shape/appearance models used in FIRST are constructed from manually segmented images provided by the Center for Morphometric Analysis (CMA, MGH, Boston). This approach is different from using a whole-structure summary measure like volume, as it allows visualization of the region of the shape that is changing as well as the type of shape change (changes in shape will be examined with exploratory analyses). Figure 5 illustrates a shape-based analysis of the hippocampus. Taken together, these analytic strategies will provide highly detailed information regarding longitudinal changes in the hippocampal structure.

Data Analyses and Specific Hypotheses

Preliminary analyses will be conducted to verify that demographics for the groups are adequately matched. If significant differences are found, these will be taken into consideration in subsequent analyses. Further, based on our previous studies indicating that target variables are normally distributed, we propose a parametric approach to data analysis; if any violations to parametric statistics are detected, we will employ corrections and/or non-parametric equivalent tests. To control for development related changes in brain maturation between the ranges of subjects, each series of analyses will treat age as a covariate. *With the exception of needing to control for any changes in aerobic fitness do to exercise activity from outside the trial (in the waitlist control) this will be the only covariate used in analyses*. For ROI based analyses, significance testing and adjustment for multiple comparisons will be calculated via modified Bonferroni correction. Only participants with no history or current treatment with antipsychotics will be included in the study. If participants begin treatment with neuroleptics during the 3-month trial period, they will be permitted to complete the trial, but excluded from the study. Our aim is **If UHR subjects participating in the exercise condition show greater post-trial increases in medial temporal volume and improved cognitive, symptom and social/role functioning profiles when**

compared with the UHR waitlisted-controls. We predict that the UHR exercise treatment group will show a strong trend to suggest larger effects for increases in hippocampal and parahippocampal gyral volume, and improvements in cognitive, social/functional and symptom profiles after the trial as compared to the UHR waitlist controls. Any naturalistic aerobic activity seen in the UHR Waitlisted-Controls will be monitored by testing for changes in aerobic fitness between the pre-post 12-week assessments (although we do not anticipate a great deal of naturalistic aerobic activity in the UHR control group based on our pilot findings, any changes in fitness will be controlled for in the respective statistical analyses). *Any participants in the UHR exercise group that are naturalistically being treated with psychotherapy will be matched with a wait-list control participant treated with a comparable modality.* All intervention analyses in the R33 phase will be conducted utilizing random coefficient regression that controls for variability in response across participants as well as the within-subjects nature of the fitness assessment data and cognitive assessment data. This flexible mixed models statistical approach (Cohen *et al.*, 2003) allows for the inclusion of the age covariate, as well as the utilization of sophisticated approaches to the treatment of missing data (full information maximum likelihood (FIML) estimation) (Schafer & Graham, 2002). There are several important reasons for including a controlled trial phase. First, a pilot controlled trial will provide opportunity to develop consistent practices to enhance data integrity and the protection of human subjects (e.g., informed consent procedures, data collection tools, regulatory reporting procedures, procedures for adverse event reporting). Second, it will be important to determine that any effects seen across the UHR-exercise group are due to the proposed intervention and not simply reflecting learning effects (for the cognitive measures) or developmental changes. Finally, the process of conducting a small clinical trial, before disseminating the findings or planning a larger multisite controlled trial will invariably provide a number of valuable insights and unforeseen factors. This study will be instrumental in evaluating the feasibility of recruitment, retention, assessment and implementation of a novel intervention in a fully powered trial.

Exploratory: Aim A) If the intervention has an influence on course of illness and conversion rates. An important ultimate consideration for UHR individuals relates to clinical outcome or conversion to formal psychotic disorders. Within-group analyses will focus on how varying degrees of aerobic fitness, brain, and cognitive changes post trial or wait-list predict 12-month and 24-month symptoms levels and conversion status. In addition, it will be possible to compare the conversion incidence with that reported from extant well-powered studies. Finally, because there will be a small group of wait-list participants followed up (from years 3 and 4), it will be possible to run exploratory analyses to compare groups in course and outcome over time (note: those control UHR youth who elect to accept the offer to participate in the free exercise program following the wait-list period will be excluded from these analyses). Although the sample size prohibits any strong conclusions with regard to conversion (based on the current literature only 10-15% are likely to convert to psychosis), this approach will allow for us to track longitudinal changes symptoms, and social/role function and the data will be useful in determining the ultimate effects of the intervention on long-term clinical course and conversion.

Timeline, Sample Size, and Power Analysis:
Over the course of two years collecting data, 30 UHR participants (15 UHR-exercise, 15 UHR

waitlisted-control) and 15 controls will participate in the study. Based on pilot data and observations for similar trials in other clinical populations, it is estimated that there will be a 20% attrition rate among the participants. To allow for a sufficient sample size to complete the Aims we propose to overall-sample at this rate a total of 36 subjects will be recruited for the R33 trial (an extra 3 in each group).

Although the funding mechanism does not explicitly require a sample size sufficient to yield high- statistical power (PAR-11-177- *"Pilot studies are not expected to be sufficiently powered to test efficacy, and inferential statistical test are not expected at this phase of development"*), we projected the proposed numbers for each phase to provide a power level that is sufficient for detecting larger significant effects. Following Cohen's (1988) standard guidelines for power calculation (Cohen, 1988) and utilizing G*Power 3.0.3 (Faul *et al.*, 2007), we confirmed power estimates for each phase of the trial. In the R33 phase we benefit significantly from the strength of the repeated measures design. For the two-tailed multivariate tests comparing the two groups (UHR exercise, UHR waitlist-control) on target variables, with 15 participants per group and two measurement occasions, we should have observed power of .75 with α=. 05 and for the detection of a moderate effect size (f = .25). Our observed power for the detection of a large effect (f = .40) should be well over .99. Thus, while significant effects are not central to the aims of the investigation, there is still power to detect larger effects in both phases.

The scanning portion of the study will take place at the Center for Translational Imaging (CTI) located at 737 N. Michigan Avenue, Suite 1600 Chicago IL 60611. The MRI device for these scans is FDA approved for research with human subjects and has all the safety inherent in a clinical MRI scanner. The radio frequency fields conform to guidelines determined by the FDA and the FDA has designated MRI scanners to be a non-significant risk device. MR techniques non-invasively produce images and measurements from tissues in the intact, living human. The facility houses Tim Trio 3.0 Tesla Siemens Medical Solutions scanners.

About the Subjects

The participants in the proposed study will consist of 30 UHR youth (15 in the exercise and 15 in the waitlisted-control) and 15 HC. All participants (age 16 to 24) will be recruited into the study over a 5-year period through the established Adolescent Development and Preventive Treatment (ADAPT) program directed by Co-P.I. Mittal. Potential UHR subjects undergo a telephone screen and those who screen positive will be invited to an in-person eligibility and consent evaluation. Those screened participants who meet criteria for a prodromal syndrome based on the SIPS (Miller *et al.*, 2003a) will be invited to participate in the study (help-seeking individuals who do not meet criteria will be referred to appropriate community resources). This upper limit of 24 years was chosen as this age falls within the range for mean age of conversion to psychosis yet is still characterized by significant changes in neural organization (maximizing the potential for the trial to influence brain morphology) (Sowell et al., 1999). With regard to physical activity status, consistent with previous exercise studies, all participants will be sedentary. HC participants will be self-referred (responding to flyers and ads).

For the scan portion of the study, in order to protect the health and safety of the participants, exclusion criteria for this study will include any contraindication to magnetic resonance scanning (e.g., metal in body, claustrophobia, pregnant). These exclusions are specific to MRI and are consistent with most studies involving MRI. Potential participants will be screened for the presence of any of these exclusion criteria prior to participating in this MRI study.

Financial Compensation

Participants will be given $45.00 for 1.5 hour screening to decide whether they are a good fit for the study. If found to be a good fit, participants will be given an additional $30 per hour for up to 3-hours of clinical assessments. UHR participants will be given $45 for a 1.5-hour cognitive battery. For the scan, UHR subjects will be given $45 for 1.5 hours and HC participants $60 for the 2 hour scan. For the fitness assessments, UHR subjects will be given $20.00. For the exercise intervention trial, subjects who are exercising will be given $20.00 per 40 minutes of their time. Participants who consent to the blood draw will be receive $25 for each of the draws. Subjects will be asked to complete the clinical assessments, cognitive testing, and scan post exercise intervention, and they will receive the same reimbursement. Additionally, they will receive this reimbursement at 12-month, and 24-month time points. Other compensations include: 1.) To improve compliance, the exercise group will be enrolled in a rewards system. For each completed exercise session, they will receive a ticket for the total of 24 tickets. For the first 8 tickets, each participant in the exercise group will get a $50 gift card. For the next 8, they will get $100 gift card (Northwestern's PNC Stored Value Card which will be explained to participants). For the last 8 tickets, they will get an iPad mini. 2.) Snacks will be available at any of the visits and any costs relating to parking will be reimbursed. $15 will be used to purchase snacks for participants. $10 dollars will be available to supplement travel/gas costs for the Pre/Post Exercise Assessment time points as well as both the 12 and 24-month follow-ups ($40 total for participation in the duration of the study). If participants would like to complete the 12 and/or 24 month follow-up clinical assessments over the phone, they will be emailed a virtual Northwestern Stored Gift Card after completing the interview. Transportation/snack total costs will be $55. As noted earlier, we will also arrange for a free pick up and drop off service for each of the exercise sessions if requested.

Withdrawal of Subjects*

If a subject chooses to stop participating for any reason, his or her participation in the study will be terminated. Though highly unlikely, the circumstances under which a participant would be withdrawn without her consent include: (1) obviously not following study instructions or (2) behaving in a way that is verbally or physically abusive towards research staff. Those who experience early withdrawal will receive prorated payment based on the number of sessions they completed

Risks to Subjects*

Risks associated with breach of confidentiality: There is a potential risk that confidential health information collected during the course of the study may be disclosed to others.

Risks associated with stigma: There is a potential risk that participants will be subjected to stigma and undue anxiety from identification as "at risk" of a serious mental disorder.

Risks associated with being distressed: There is a potential risk that the participants may find the study questions and procedures tedious, or that they may be distressed by the discussion of personal issues.

Risks associated with the MRI Procedures:
1. The magnetic field of the MR environment has the potential to cause burns or bodily injury if ferrous metal objects are implanted in the body, or if personal articles containing ferrous material are brought into the environment.
2. The risk of MRI to pregnant women and fetuses is currently unknown.
3. The MRI may cause discomfort due to scanner noise.
4. There may be some discomfort from lying still and in one position for a long time
5. Peripheral nerve stimulation (PNS/tingling). At sufficient exposure levels, peripheral nerve stimulation is perceptible as "tingling" or "tapping" sensations. PNS symptoms will usually subside shortly after the scan is completed.
6. Participants may feel nervousness or feelings of claustrophobia.
7. There is a risk that the image will reveal an observation concerning an individual research participant that has potential clinical importance but is beyond the aims of this protocol. In the event of the confirmation of a significant anomaly in a participant's brain image, this information will likely be distressing to the participant.
8. In rare cases, MRI can result in burning or tingling sensation, skin irritation, or swelling at the tattooed areas without lasting effects or complications (MRI safety.com, 2016; FDA, 2015). One study retrospectively examining reports from 108 individuals with tattoos who have undergone an MRI scan found no complications (Nouredinne, et al., 2015). In another study, only two out of 135 participants (1.5%) reported slight tingling or burning sensation (Toppe, et al., 2002). The authors also reported that an estimate of less than 10% of individuals who have undergone an MRI scan have reported transient symptoms (swelling, heating or burning sensation, or skin irritation). In one case study that reported an athlete experiencing skin reddening and mild swelling at the tattooed areas after an MRI reported that the symptoms were resolved within 12 hours with no permanent effects (Ross & Matava, 2011). These risks may higher if the tattoo is directly in the exposure volume of the transmit coil; therefore, we will exclude participants who have face or neck tattoos.

Risks Associated with the treadmill/elliptical tests: During treadmill/elliptical tests, the American College of Cardiology/American Heart Association (2002) note that about 4 in 10,000 people will experience chest pains or a heart attack during the maximal exercise test and about 1 in 10,000 people may actually die from cardiovascular related problems during a maximal exercise test. Experiencing syncope during a maximal exercise test is more common, occurring in about 1 in 100 people. In addition, the treadmill test can cause dry mouth, fatigue and minor muscle and joint discomfort, as well as possible soreness or injury.

Risks associated with the aerobic exercise and/or stretching and toning interventions. Participants will be informed that any time they are physically active (in this case, during the supervised physical activity sessions) there is always a risk for muscle soreness and discomfort both during and after exercise activities.

Risk associated with blood draws: pain, a bruise at the point where blood is taken, redness and swelling of the vein and infection, and a rare risk of fainting.

Since we will be evaluating and monitoring subjects for the presence and the development of a psychiatric disorder, we have instituted procedures for the management of anticipated clinical issues.

Management of Risks:
Limits to confidentiality will be detailed on the consent/assent forms and will be discussed explicitly in the initial interview. Specifically, subjects will be informed that they will not be asked specifically about any illegal activities, but if they should discuss such activities, the information could be requested by authorities such as the police or court system. In addition, they will be told that there are limits to confidentiality, including our requirement to report information about: child abuse or neglect, a crime that the subject plans to commit, or harm that may come to the subject or others. With respect to child abuse or neglect, research staff will comply with state laws and complete a child abuse report with the state Department of Child Protective Services. If there is risk of harming self or others, research staff will take necessary actions, including notifying significant others who may assist in the protection of the subject's safety or notifying others who might be affected, such as intended victims, or notifying the police.

Risks of stigma and undue anxiety from identification as "at risk" of a serious mental disorder will be minimized in the following ways:
a. Information regarding possible outcomes and causes will be routinely provided. Subjects will be informed about possible outcomes, including remission, persistent symptoms, or worsening of symptoms. They will be informed that causes of symptoms include a normal adolescent or early adult maturation, a reaction to a life stressor, a symptom of drug use, symptoms of a metabolic disorder, the symptoms of a mood disorder or anxiety disorder, or the early warning signs of affective disorder or schizophrenia.
b. Study participants who are judged to be in need of psychiatric or psychological evaluation/treatment, and are not currently receiving treatment, will be referred as clinically indicated.
c. In addition, to minimize risk of undue anxiety related to uncertainty of diagnosis at screening we will also conduct a careful systematic diagnostic interview (the Structured Clinical Interview for DSM IV, SCID) and cognitive evaluation to determine whether there is an active diagnosable condition.

The risk that the subjects may find the study questions and procedures tedious, or that they may be distressed by the discussion of personal issues will be minimized by having a study staff person monitor the subject's experiences during the study procedures, and by having a study clinician familiar with the participant available to assist the subject if she or he becomes distressed by study procedures. In addition, participants will be told that they may decline to answer any questions or discuss any issue if they do not want to or if they find it distressing. Efforts will be made to make the study assessment procedures and exercise intervention as pleasant as possible for the subject, and to detect and address any problems with evaluation procedures.

This protocol will be performed using an MR scanner employing pulse sequences and hardware that have been approved by the FDA for human clinical use. There is no known radiological risk of MRI scanning. Participants will be carefully screened to exclude those who may have metal in or on their bodies that cannot be removed (e g., bullets, metal filings, body piercings, etc.). MR Facility rules strictly forbid staff from entering the magnet room carrying metal objects. The risk of claustrophobia is minimized by screening subjects for self-reported claustrophobia and making sure the subject is lying comfortably with head and neck supported and providing ear protection with headphones, a mirror to see out, a button to signal distress, and an intercom. Scan time will be kept to a minimum. Although there are no know risks to unborn fetuses, pregnant individuals are not permitted in the scanner. We will follow CTI's protocol for ruling out pregnancy: safety screening (please see supporting documents) is administered right before the scan even if the participants filled the form out beforehand. The form includes "are you pregnant?" question, and the scanning technician will not scan anyone who know or think they may be pregnant. Participants will also be reminded that they can discontinue participation in the study at any time and need not divulge to the researchers the reason for their discontinuation (i.e., if they determine they are pregnant, they need not disclose that information). Scan time will be kept to a minimum and will not exceed the noted time allotment. All participants will be screened for tattoos. Participants will be made aware of minimal risks associated with tattoos in MRI scanners and asked to inform the MR technician if they start feeling any sensation at the tattooed area. If they report any sensation, the tech will stop the scan immediately to avoid potential skin irritation and burning and tingling sensation at the tattooed site. With regard to PNS, participants are given a squeeze ball to use in case of an emergency. They are informed that if they experience PNS related sensations or are otherwise uncomfortable, they can alert the MRI technologist via the squeeze ball and the technologist will stop the scan immediately.

These risks associated with blood draws are minimal, and are reduced in this study because trained personnel who have extensive venipuncture experience, and are trained in aseptic technique, will implement the blood drawing procedures in a clean room.

Steps to ensure safety with regard to the potential risk from study participation have been noted below. The sample size does not allow for adequate power to make specific estimates with regard to how the frequency of any adverse events from the exercise trial would carry over into a larger trial (Leon et al., 2010). In addition it should be noted that previous studies of aerobic exercise interventions including Dr. Mittal's have shown minimal adverse events.

A number of steps have been taken to safeguard privacy and confidentiality across the study. All study staff will be required to sign statements indicating that they understand confidentiality and agree to protect against risk of confidentiality. During phone screening, participants will be asked at the start of the phone call if they are able to speak privately, and if not, will be offered an opportunity to reschedule the phone call. Project staff will use private offices and a private voicemail has been established specifically for screening (and recruitment) of clinical studies such as this one. Only project staff will have access to the voicemail code to access messages. In the Zoom version of the 12 month follow up interview, IRB approved study staff conducting the assessment will store the video locally on encrypted, locked hard drive. For Zoom follow ups,

staff will ask the participant ahead of time to secure a private, quiet place where they can talk about their thoughts, feelings, and experiences without violating privacy.

With regard to the minimization of risks specific to exercise training, all participants will be phone screened for contraindications related to physical activity generally and to the maximal exercise test in particular. In terms of the risks related to the maximal exercise treadmill test, the primary protective measure taken to assure the physical safety of participants is the test location. The American College of Sports Medicine certified exercise physiologist, Elizabeth Skender will be present for all of the maximal exercise tests. Elizabeth Skender's ACMSM certification number is 1043289. In addition, she is and Advanced Cardiovascular Life Support (ACLS) provider (please see her certifications under supporting documents). If any exercise physiology or research personnel have any concerns about the participant's health or safety during the maximal exercise treadmill test, the session will be terminated immediately. The following specific protective measures will be taken for all participants: (1) Participants will be asked during the initial phone screen if they have any history of cardiovascular or respiratory disease so as to decrease the risk of a participant experiencing cardiac problems during physical activity. (2) During the phone screen, participants will be asked prior to the maximal exercise test to assure that they have no undiagnosed medical contraindications that would make it dangerous for them to participate in either the maximal exercise treadmill test or the aerobic activity interventions. (3) During the maximal exercise test, the participant's heart rate and EKG will be monitored to assure that they are not experiencing an adverse cardiac event and to assure that they are healthy enough to safely participate in a moderate to vigorous intensity aerobic exercise program after the test. (4) Automated external defibrillator (AED) is available on site, and the exercise psychologist is trained on ACLS. No medical personnel presence is necessary during the VO_2max test.

With regard to risks related to exercise during the supervised exercise sessions, all participants participating in the exercise interventions will receive individual instruction regarding safe exercise practices by our exercise physiologist. The structure of the aerobic exercise intervention, which is quite standard in exercise training interventions to improve cardiovascular fitness, is designed so that participants gradually work up to their training level of intensity. Further, exercise prescriptions are tailored to each participant's current level of cardiovascular fitness. Because participants begin slowly and move gradually up to the recommended level of exercise, and exercise takes place under close supervision of trained exercise physiology and exercise research personnel, the potential for injury during exercise should be minimized for this study.

Only low risk participants will complete the exercise study. The young adult and adolescent populations are at low risk for heart attack or exercise related injuries, and as noted throughout the protocol, the pre-screening questionnaire includes questions which exclude individuals who may be at a higher risk from the study. Participants will receive instructions that they should: 1) wear appropriate exercise clothes and shoes for testing; 2) be well nourished and hydrated prior to testing; 3) avoid alcohol, caffeine and tobacco within 3 hours of testing; 4) be rested and avoid significant exertion or exercise the day of testing; and 5) report any medication use to the testing staff prior to testing. Participants will warm up prior to testing and cool down after testing. Standard emergency procedures will be followed in the event of an emergency. Masks and

mouthpieces are disinfected between participants. Participants will be monitored at all times during the VO2max test by at least one technician or team member who is knowledgeable and trained in two specific areas: 1) administration of graded exercise tests, including ability to conduct pre-test health screenings, and knowledge and recognition of signs and symptoms of cardiovascular disease; 2) procedures for conducting metabolic measures. In addition, the exercise physiologist will monitor all exercise visits, and as noted, she has all the necessary training to provide life support in a case of an emergency. Moreover, the automated external defibrillator (AED) is available on site, and campus police, who are located two floors below are lab, can be reached in a case of an emergency. Test termination criteria include any of the following: subject requests to stop, physical or verbal manifestations of fatigue, failure of test equipment.

Procedures for the management of anticipated clinical issues include the following:
a. As noted a legal guardian of the participant (for minors) or the participant (for adults cases), will be screened over the telephone. Individuals will also be notified in advance beginning screening of the limits to confidentiality. During the phone screening process, a number of steps will be put into place to protect against clinical risk. If a caller expresses non-emergent mental health needs, research staff will provide this person with the phone number of the behavioral health clinic and instruct her to call to set up an appointment. If over the course of the phone interview the caller becomes emotionally distressed, is not making clear sense, sounds intoxicated or impaired, or expresses thoughts of suicide or homicide, the interviewer will use a second phone line to have the study investigator join them, without losing verbal contact with the participant. At that point the study investigator will guide the interview to ascertain the acuity and/or potential for harm. The study investigator will first determine if the caller is alone or has access to another person capable of transportation. If the study investigator determines that the individual is in need of emergent care, the options for such care will be discussed with the caller and may include – referral to the closest emergency room, notification of emergency services for transportation to ER, emergent appointment (that day). If the subject declines such a referral, the emergency services will be notified of the clinical concern for safety. b. If at the initial in-person screening visit the subject that is found to have a medical condition that may have caused the prodromal symptoms, they will be excluded from further participation. If either an exclusionary medical condition or an incidental medical condition is suspected, the participant will be advised to consult with their physician or referred. If a psychiatric disorder is found to be present at baseline, or is found to develop during the course of the study participants will be advised to consult with their mental health care provider or referred. These participants will continue to be followed in the study, with information on treatment recorded in the database. Minor subjects and their parents or guardians will be informed that we will be doing urine drug screens as part of the routine study evaluations. We will explicitly inform parents and potential minor subjects, in the written informed consent document and orally, that we will not inform the parent of the results of the drug test, because revealing this information could affect the willingness of the minor subject to participate in the study or answer truthfully. We will tell both the minor subject and the parent or guardian our clinical policy regarding confidentiality, as follows: If a minor subject is found to have a positive drug screen, the PI will discuss the risks of drug use with the subject, and encourage the minor subject to discuss their use of drugs with their parent or guardian. If the subject is found to have a substance use disorder, we will discuss the need for treatment with the subject, and encourage the subject to allow us to speak with their parent or

guardian about our concerns. The University's IRB has approved this procedure and it has been affective in our ongoing studies of UHR individuals. Participating minors will be informed that their parents will be notified in the event that they are engaging in or plan to engage in behavior (i.e., suicidal attempt) that is dangerous to themselves or others. e. To summarize, our procedures will follow routine clinical research procedures to reduce risk to participants, and follow all State regulations regarding treatment of minors and informing parents and guardians. A single clinician attempts to engage the minor in a therapeutic relationship, and maintains confidentiality unless there is a specific, immediate safety risk (e.g., suicidal ideation).

Drug testing

Participants will be informed "You will be asked questions about illegal activities that he/she/you may have been involved in. Although it is not likely, it is possible that their/your answers could be requested by the police or the courts and used against them." Otherwise, results of drug tests will remain confidential.

Thoughts of Suicide

We will carefully monitor suicidality throughout the study, and the investigators and the clinical services are well equipped to handle psychiatric emergencies. Specifically, all research assistants are provided ongoing education and supervision with respect to the identification of potential clinical problems. In addition, all are educated to have a very low threshold for obtaining consultation. In addition, Dr. Mittal will carry a mobile phone listed with all study staff to be available 24/7. We will have available 24/7 on call and emergency services. Additionally, Dr. Molly Lubin will be available for clinical guidance and consultation. Potential suicidality will be queried for all subjects within the context of the noted clinical interviews and patients will be carefully observed when participating in the exercise trial. If suicidality is present, gold standard procedures will be implemented (i.e., determining if a plan or means are available, contracting for safety, informing parent/guardian of risk (in the case of minors), ensuring removal of any potential means or in severe cases encouraging self-hospitalization/requiring involuntary hospitalization. In the case of minors for voluntary or involuntary hospitalization, participants will be escorted to the Evanston Hospital. For Zoom follow up, the assessor will collect current location and phone number to protect against risk during remote assessment. The current location and phone number information will be discarded as soon as the interview is completed. This information will be necessary in the situation that gold standard procedures need to be implemented remotely.

Training of Staff

All research staff will be trained in the regulations governing the conduct of human subjects research, as well as HIPAA regulations. All investigators and consultants have passed the IRB examination, which requires knowledge of basic ethical principles and federal regulations concerning human subjects research. Investigators will assure that all research assistants complete the same training.

All clinical evaluators will receive intensive training prior to conducting phone screens or assessments with study participants. In addition to training on the specific measures, training will include education about orientation to the assessment process, possible risks to participants, and

an extensive 2-month training period for phone screens and assessments (observing live interviews with trained raters) observed by investigators. As reviewed above, we plan to hold weekly meetings involving related project faculty and staff to review assessments and cases and discuss any clinical issues (note: the exercise physiologist, who will be aware of which participants are in the treatment groups, will not participate in these meetings to maintain blindness). Separate weekly meetings will be held with the exercise physiologist to track progress, discuss motivation and attenuation or participants, and address any clinical/safety issues.

Protection against Risk associated with the Ultra High-Risk Waitlisted-Control Group Assignment

We have taken careful steps to minimize potential risks associated with assignment to the control group. Because of the critical period associated with the prodrome, all UHR participants will be encouraged to maintain any concomitant treatments already in place or referred to appropriate treatment providers in the community if they are not already receiving any treatment (Note: this is standard procedure in all current treatment and naturalistic investigations of UHR youth). As noted, individuals with a history or current treatment with antipsychotics will not participate in the study and those naturalistically treated with psychotherapy will be balanced between the two groups. Concerns regarding the withholding of an active intervention are mitigated by the treatment development nature of this project and our lack of knowledge at this point regarding the efficacy of the exercise-intervention approach. However, while the proposed exercise trial has not been proved to be efficacious, participants and parents will likely wish to participate in anything that is potentially helpful during this critical risk period. To address this concern, we will offer the UHR waitlisted-controls the option to also receive 12-weeks of exercise immediately following the waitlist period (that is immediately following the post interviews. Participants are also invited to engage in the exercise portion at any point after these post interviews even before or after the 12 and 24 month visits). Although there will be no research questions tied to this option (there will be no additional assessments or time-compensation given post-waitlist period) the participants will have the chance to participate in supervised aerobic exercise. This will allow for the UHR controls to benefit from any potential positive effects associated with an aerobic intervention. As noted, should any individuals elect to take this option, they will be excluded from longitudinal follow- up analyses examining the effects or exercise/waitlist on clinical course/conversion outcome.

Potential Benefits to Subjects

Anticipated benefit to subjects and/or society is a greater understanding of the factors that influence risk of development of a psychotic illness. In addition, participants may benefit directly from the exercise intervention.

Consistent with the ethical obligation to the participants, we will provide information about community treatment resources for those who are deemed in need, but are not currently receiving clinical care. At the initial assessment and post-intervention assessment the participant will be asked to provide information on treatment history. For minors, parents will also be asked to provide this information. The following data will be collected; previous and current treatment counselors or mental health providers, psychotropic medications prescribed, current medication, and diagnoses.

Assessment results from each participant will be discussed in a weekly research meeting with Graduate Research Assistants and Drs. Mittal and Lubin. In cases where the results suggest the need for further treatment and the participant is not currently under the care of a mental health professional, the participant (parent for minors) will be provided with a list of mental health care professionals in the area who have the necessary expertise. Any participant found to be suffering from an Axis I psychotic disorder at the initial assessment will not be included in the study and as noted, referred to appropriate treatment in the community. It should be noted that prospective participants and parents who contact our center usually have serious concerns about their or their child's adjustment. The findings from previous research in this population suggest that these concerns are often warranted. Specifically, research has shown that treatment for psychosis generally leads to a good outcome when the treatment is initiated "at onset" – meaning as soon as frankly psychotic symptoms are detected in the context of regular monitoring visits. Generally it is possible to treat such patients as outpatients without loss of days of work or school, without disruption of ongoing social networks, and without the development of potentially stigmatizing events such as frankly abnormal behavior or hospitalization (Haroun et al., 2006; Corcoran et al., 2010). In line with the proposed protocol, treatment guidelines for the prodrome are just beginning to emerge and currently recommend that the patient be carefully monitored, but that antipsychotic or other medication treatment not be initiated, as there are no data regarding the risk-benefit ratio, and the risks of antipsychotic treatment in particular may be substantial in this population (McGlashan et al., 2007). Thus this proposal is consistent with current clinical practice guidelines. While data from ongoing prodromal studies are now emerging to address this issue, further research is needed before practice guidelines for treatment of the prodrome will be established. It is unlikely that empirical data will be available for expert consensus panels to address the issue of treatment of the prodrome before this project is completed. Furthermore, we anticipate that the results of this study would contribute to such guidelines by informing the discussion of characterizing high-risk individuals where a targeted intervention would be of highest value.

Importance of the Knowledge To Be Gained

The results of this study will increase ability to understand etiological factors in high-risk individuals prior to the onset of schizophrenia or other psychotic disorders. In addition, we will be testing the feasibility of a potentially helpful exercise intervention. Improved comprehension of this group will facilitate future preventative research. Intervention in early psychosis is of tremendous potential public health importance and thus the risk involved in this observational study are relatively small in proportion to potential impact on treatment of psychosis.

Additionally, all participants will have the opportunity to examine their own exercise behavior in the context of completing the measures. Further, participants will learn about their maximal oxygen consumption, a measure of their aerobic exercise capacity and current level of aerobic fitness. Participants will have their cognitive functioning assessed by experts both in terms of brain physiology and cognitive tests. For the older adults in this study, both interventions (aerobic and strengthening and toning) are designed to increase health. Thus, regardless of which condition participants are randomized to be in, participants will gain information about their health and engage in healthy behaviors by completing the requirements of the study. The minimal costs associated with participation in this research seem reasonable in relation to both

individual benefits to the participants as well as the anticipated potential of the findings to increase the body of knowledge about the mediators and moderators of exercise behavior change.

Vulnerable Populations

This research program will be treating and studying persons who are at risk for developing schizophrenia or a related psychiatric disorder. However, it is not possible to study psychiatric disorders without studying individuals who have the psychiatric disorder being investigated. Additionally, based on our aim to study the prodromal period of psychotic illness, we will focus on adolescent and young adult subjects. Given that the risks involved in the measures of this program are minimal, and that the data derived are anticipated to be extremely useful for improving our understanding of the disorder and develop a potentially important treatment, we believe that the involvement of these UHR patients is justifiable.

Sources of Materials

Sources of material will come primarily from the participant, in the form of the results of questionnaires, clinical interviews, neurocognitive battery, and neuroimaging. For minors, a parent/legal guardian will provide information. Biological specimens will be collected at screening (urine) to help determine recent substance use. Written and oral consent will be obtained from participants, or their legal guardian for minor participants. Assent will be obtained from minors. These measures are described in greater detail in the body of the proposal. All materials are obtained for research purposes. Procedures for maintaining confidentiality, including linkage to participants and access to identifiers are described below under "Minimizing Risks to Confidentiality."

Provisions for Data and Safety Monitoring of Participants

As noted, there will be weekly meetings with the clinical and exercise staff (separately) to discuss case progress and any potential clinical issues, or complications relating to exercise (e.g., sore muscles, aching joints, trouble breathing, dizziness). The PI-s will be responsible for monitoring and reporting any clinical or exercise related adverse events.

Data Safety Monitoring Plans

Symptoms and diagnosis will be evaluated as part of the study during the visit (and throughout the visit this information will be collected), and in the event of any concerning symptoms or diagnostic status, an ADAPT assessor will contact the family (if the patient is younger than 18), the patient (if the patient is older than 18), and the outside treatment team for the respective individual. The trained assessor will carefully review each case and discuss details with the PI. Data will be reviewed after each visit. If a patient reports suicidal ideation at any time during a research assessment, referrals, and if needed, appropriate recommendations of inpatient care to insure the safety of the subject will be made. If the subject is a minor, the participant's legal guardians will be informed, and a safety plan will be established. If inpatient care is needed immediately, 911 will be called, and the assessor will wait with the participant until someone takes them to the Northwestern Hospital. All ADAPT personnel are trained in assessing for suicidality and are required to consult with a licensed treatment provider on staff to ensure adequate assessment. Additionally, if inpatient care is not warranted, ADAPT staff are trained to make "contract agreements" with participants for their safety and follow-up with the participant to continue to assess for safety.

Suicidal Thoughts

We will carefully monitor suicidality throughout the study, and the investigators and the clinical services are well equipped to handle psychiatric emergencies. Specifically, all research team provides ongoing education and supervision with respect to the identification of potential clinical problems. In addition, all are educated to have a very low threshold for obtaining consultation. In addition, Dr. Mittal will carry a cell phone listed with all study staff to be available 24/7. We will have available 24/7 on call and emergency services. Potential suicidality will be queried for all subjects within the context of the noted clinical interviews. Specifically, the BDI-II will be scored before the participant leaves the laboratory. If participants endorse current suicidal ideation on item 9 of the BDI-II, a clinical psychology graduate student will complete a suicide assessment. The BDI will be scored directly after the assessment, while the participant is in the room. Scoring item 9 on the BDI takes no time at all – about 30 seconds in which the assessor looks at what number was circled (2="I would like to kill myself" in which case the assessor will know to move forward accordingly). The assessor will let the participant know they are just reviewing everything briefly while they look over the BDI and other notes if needed (just in case the assessor needs additional information). Upon completion of this assessment, student clinicians will collaborate with the PI Mittal (a licensed clinical psychologist) to decide on a plan of action before allowing the participant to leave the laboratory. If suicidality is present, gold standard procedures will be implemented (i.e., determining if a plan or means are available, contracting for safety, informing /guardian of risk (in the case of minors), ensuring removal of any potential means or in severe cases encouraging self-hospitalization/requiring involuntary hospitalization. The student co-investigator (Tina Gupta) has been trained on conducting suicide assessments. If the student judges a participant's suicidality to be mild or moderate, and determines that the participant is not in imminent danger, then the student clinician will provide the participant with information to local low-cost/sliding scale treatment providers. In cases of high-risk (i.e., a specific plan, a means to achieve the plan, no-one else in the residence to monitor the individual or provide a safety network) voluntary or involuntary hospitalization will be directed to the Northwestern Hospital, which has a world-class adult psychiatric unit. Acute suicidality has been rare in our ongoing studies with this population (although SPD and FEP individual commonly show depressive symptomatology including symptoms of suicidality), but these noted procedures and precautions have proved effective in our ongoing work with psychosis samples. This plan can also be done remotely during the Zoom follow up assessment as referrals will be available electronically for those who are not in imminent danger. For high-risk cases, the participant's current location is collected immediately before the remote interview by the interviewer, and the nearest appropriate medical center will be substituted for Northwestern Hospital.

Confidentiality and Data Management

Strict standards of confidentiality are maintained. All paper records (consent forms and SIPS) containing identifying information (including the subject contact list) and all subject videotapes will be stored in a locked file in a locked office in ADAPT program at Northwestern. All data is given a deidentified ID code. All electronic databases will have deidentifying information and be password protected/encrypted. Deidentified data may be shared with other researchers to advance science, as specified by the updated Northwestern IRB consent form template. Subjects will remain anonymous in all datasets and subsequent publications. Unless Northwestern IRB

approval is sought and obtained to extend the period of data storage, data will be stored for 30 years after study completion and then destroyed. Videotapes will be stored for 30 years after which point they will be destroyed unless individual approval is sought to continue their storage and use for teaching and research purposes.

Confidentiality will be maintained by assigning each patient a study number, and coding all data collected with that number. Identifying information will not be stored on computer databases, and will not be stored with the study subject number. All computer databases are password protected, and hard copies of all data and records will be stored in locked filing cabinets. All study personnel will be certified to conduct research with human subjects, and will be aware of the importance of maintaining strict confidentiality.

Cortisol samples will be labeled marked by the appropriate subject ID number and 1, 2, 3, 4 (e.g. 5555-1, 5555-2, 5555-3, 5555-4). The take home samples will be labeled with the subject ID number followed by a 01, 02, 03, 04, 05, 06 (e.g. 5555-01, 02, 03, 04, 05, 06).
II.
Strict standards of confidentiality are maintained. MRI data will be electronically stored and analyzed using ID codes. If the data are published subjects will remain anonymous in all publications. Data will be stored indefinitely and will not be shared with other investigators without explicit permission from the Northwestern IRB. All imaging data and behavioral data will be uploaded to the Northwestern University Research Image Processing System (NURIPS), an online collaborative research environment for securely storing, managing, analyzing and sharing de-identified medical imaging, associated data (e.g. behavioral), and results from advanced customizable processing pipelines. NURIPS is supported by both NUIT and FSM-IT and takes advantage of the NU high performance computing cluster, Quest. NURIPS is a secure environment that supports the latest NU policy and procedures for encryption of data during transit and rest, provides granular project level access controls with varying permissions based on user groups, and allows non-NU collaborators access once they obtain an affiliate NetId. All data are backed up and have restore points that go back for 30 days. Users have access to common data analysis pipelines and the opportunity to create and share their own pipelines.

All instances of shared data within this protocol will be specifically approved by the IRB, and will be noted in the consent/assent forms, including how and what information will be shared. Subjects decide if they would like to share their data with other investigators. Every consent form has check boxes included to allow for this.

Basic identifying information (name, address, phone number/email address) is collected from every research participant for the purpose of research logistics (schedule visits, etc.) and mailing of the radiological review letter, as appropriate.

Provisions to Protect the Privacy Interests of Subjects
Prescreens: In accordance with Northwestern IRB's guidelines for pre-screening potential participants only first names or initials will be collected to identify the potential participant during this phone screen (prescreen). In order to protect participant confidentiality, the

first five pages of the phone screen form will be shredded immediately after the phone screen (pre-screen) is complete. Only the information relevant to contacting the participant on the last page of the phone screen will remain. This contact information will be important for the study team to retain so that we will be able to contact participants concerning their study appointments. Participant contact information will be stored in a separate research folder, apart from all other study documents. This folder will be stored in a locked filing cabinet in the ADAPT lab. Upon study closure, all contact information sheets will be shredded. At the end of the phone screen session, eligible individuals will be provided with a detailed description of the study. These eligible individuals will be made aware of the required laboratory sessions, supervised exercise sessions, physiological measures, psychological measures, and potential risks involved with participation. Eligible individuals who verbally indicate their willingness to participate in the research will be scheduled for a baseline appointment. Upon scheduling a baseline appointment, potential participants will be provided, via e-mail attachment or hard copy mail (depending upon their preference), a letter that will include the time and date of their appointment, as well as information detailing the American College of Sports Medicine (ACSM) 9th edition guidelines for participating in a maximal exercise test. Once potential participants arrive for their baseline appointment, they will hear a presentation about the research program and will have the opportunity to ask any questions they have about participating. Once all of their questions have been answered, potential participants will be asked to carefully read an informed consent document. The informed consent form will reiterate the experimental procedures, monetary compensation, risks and benefits, of all data obtained, and the voluntary nature of all components of the study. If participants agree with all of the information in the consent form, they will be instructed to sign their name on the space provided indicating they consent to participate in the research.

For 12 and/or 24 month follow-up clinical assessments that take place over the phone, the assessor doing the assessment will talk to the participant in a private room at the 1801 Maple Avenue ADAPT lab location to ensure privacy during the phone call.

Setting

As noted above, participants will call in for a phone screening. If they are found to be a good fit for the study, the will be asked to come into the lab located at 1801 Maple Avenue, suite 3120 Evanston, IL 60201. The VO2max test will be taken place Northwestern University, Department of Physical Therapy and Human Movement Science, 645 N. Michigan Ave. 10th Floor, Chicago IL 60611. The MRI scan will be taken place at CTI located at 737 N. Michigan Ave, Suite 1600 Chicago IL 60611.

Resources Available

All individuals that will have direct contact with participants that are minors are trained and skilled in administering the primary interview named the SIPS. PI's and Co-PI's have had several years of experience working with UHR youth and dealing with various situations. After each case, the assessor will discuss the details of the case with the PI of the study, an expert in working with UHR participants. Reliability checks of the SIPS interview will occur often in order to make sure assessors are adhering to interview standards.

Our research lab is completely private. Food, snacks, water, and magazines are available to participants in order to create a comfortable environment. If participants would like further resources, they will be referred to other health care providers that may be a good fit for them.

All new assessors upon the approval of the study will be given a copy of the protocol to review and study. They will have a meeting with the PI to discuss details such as study procedures, and confidentiality to ensure they understand their role and the study protocol. Additionally, they will have CITI training complete in order to begin working with participants.

Recruitment Methods
We will be using ads on Craigslist and job search engines, flyers, and brochures for recruitment. We will utilize flyers in Spanish for referrals but are recruiting only English speakers (e.g., a Spanish speaking individual who may want to refer an English speaking family member or friend). If a participant who is not a minor with a Spanish speaking family member or a friend wishes for that individual to accompany them, we have a fluent Spanish speaker (Teresa Vargas who is native Spanish speaker) on the research team who can translate pertinent aspects of the study (e.g., time commitment, type of tasks administered) and answer questions. If the participant agrees, she can also inform them about participant's progress and referral sources. We also aim to recruit via social media networks (e.g., Facebook) by posting ads in social media groups (please see a script in supporting documents), electronic dissemination of ads via email, Pandora Radio ads, Psychology Department's paid research registry, and ADAPT's website (the website will include the note we are recruiting for the study and a webpage where participants can express interest in participating by responding to a Qualtircs survey asking them to respond if they are 16-24 and to provide contact information for a study team member to contact them).

Phone Screening:
A legal guardian of the participant (for minors) or the participant (for adults cases), will be screened over the telephone by an experienced staff member about, 1) the presence of prodromal symptoms in the past month; 2) past treatment for a psychiatric disorder; 3) presence of an exclusionary neurological medical condition; and 4) age. Patients who are likely to meet study inclusion criteria based on the results of the screen will be invited to the research center for consent procedures and the screening evaluation. Those persons who do not meet criteria for a prodromal syndrome (e.g., having minor symptoms, or meeting criteria for a psychotic disorder) will be referred to appropriate treatment sources in the community. Minor subjects that self refer or are referred from a health-care provider will be required to bring a parent or guardian with them to the initial consenting visit. On initial in person screening the purpose of the study will be explained. Individuals who are interested in participating in the study will receive more detailed information, both orally and with a written informed consent. Children under the age of 18 will provide written assent, and written parental consent will be obtained for their participation.

Consent Process
A legal guardian of the participant (for participants under age 18) or the participating probands will be screened over the telephone for, 1) the presence of prodromal symptoms in the past month; 2) past treatment for a psychiatric disorder; 3) presence of an exclusionary neurological medical condition; and 4) age. Patients who are likely to meet study inclusion criteria based on the results

of the screen will be invited to the ADAPT lab for consent the study. Minor subjects that self refer will be required to bring a parent or guardian with them to the visit.
During the consent process, the purpose of the study will be explained. Individuals who are interested in participating in the study will receive more detailed information, both orally and with a written informed consent. Children under the age of 18 will provide written assent, and one parent that is competent, reasonably available, and shares legal responsibility for the care and custody of the child will provide written permission for their child to participate. If the potential participant is an adult, they will read over the consent form and sign when they are ready. Consent procedures will not be rushed. We expect participant to complete consent after about 30 minutes, however we will let participants know that they are welcome to take their time. Additionally, participants will be reminded that the study is completely voluntary, and they are welcome to withdraw from the study at any point. Participants will also be informed that being videotaped is completely voluntary as well.

Online Consent/Assent. For the optional online 12 month follow up offered to CHR participants, we will use Qualtrics to obtain the electronic signature of the adult (for those 18 years of age or older) or the electronic signature of the parent/legal guardian and of the minor (for those less than 18 years of age). An IRB approved study staff member will assess for attention and comprehension of the document over the phone or on Zoom, based on participant preference. We will coordinate the online consent/assent over email by scheduling a time to talk and by sending a Qualtrics link with a password to their consent/assent form. For minors, we will require the parent/legal guardian be present for the whole meeting to assess both people's comprehension of the document before the e-signature is acquired by both minor and parent/legal guardian.

Consent forms will be written in language that is comprehensible to individuals that have at minimum an eighth grade education. The consent form will contain information about the nature of the study. In providing participants with information about the research, there are two chief considerations; 1) to minimize psychological discomfort and potentially damaging negative expectations, and 2) to provide information that is based on the best currently available scientific data. The PI of this project, and Co-I's have considerable experience with strategies for informing potential participants about the purpose of the research and for minimizing distress and anxiety. We explain that some individuals experience changes in their perceptions, thinking, emotions, or behavior. While some are not bothered by these changes, others may find them distressing because they interfere with their ability to function. We then explain the possible reasons for such changes, including that they may be part of normal adolescent/young adult development, a reaction to a life stressor, symptoms of drug use, symptoms of a metabolic disorder, symptoms of a mood disorder or anxiety disorder, or the early warning signs of bipolar disorder or schizophrenia. We then discuss the possible course of the "changes", including that symptoms/signs often go away, remain stable, or worsen, particularly if they are the early signs of a disorder.

In order to minimize subject discomfort and attrition, it will be important to reduce the burden of participation in the study. As described in the protocol, the full assessment will take about 2 hours. Within the constraints of the research design, efforts will be made to accommodate participants' schedules and, when indicated, to avoid fatigue (e.g. breaks).

It is relevant to note that potential prodromal participants are usually experiencing subjective distress and are therefore motivated to take part in the clinical research assessment. Similarly, their family members typically encourage them to participate and are readily engaged in the assessment process.

Additionally, in the consent forms, we have used the term "thought disorder" to minimize stigmas that may be associated with using the phrase "at risk for psychosis," and to avoid distress that can accompany the phrase as well. "Thought disorder" and "prodromal symptoms" are interchangeable

In order to minimize subject discomfort and attrition, it will be important to reduce the burden of participation in the study. As described in the proposal, the full initial assessment will take about 6.5 hours total: 3 hours for screening visit/clinical interview, 2 hours for the cognitive assessment, 30 minutes for imaging and 30 minutes for the aerobic fitness evaluation. The post exercise trial will take 5 hours (the 1.5 hour baseline screening which involves providing study information, signing consents, getting background information, and diagnosing a prodromal syndrome will not be included, but participants will be administered the entire SIPS and SCID post intervention to track changes in symptoms and clinical status). Based on our experience in working with UHR adolescents and young adults, this time-requirement will be entirely feasible. Within the constraints of the research design, efforts will be made to accommodate participants' schedules and, when indicated, to avoid fatigue. As noted, our group has significant experience in working with this population, and has perfected a number of effective strategies to ease burden and strain on participants and their families (e.g., schedule breaks, snacks, reimbursement of travel/lunch/parking costs). The exercise trial will require 30 minutes of cardiovascular exercise. The exercise prescription will be tailored to the current fitness level of the participant, and the same research personnel will supervise the participants at each session to increase comfort. Finally, upon scheduling their fitness assessment, participants will be provided a letter that will include the time and date of their appointment, as well as information detailing the American College of Sports Medicine (ACSM) 9th edition guidelines for participating in a maximal exercise test. Once potential participants arrive for their appointment, they will hear a description of the fitness assessment, and will have the opportunity to ask any questions they have about participating their participation.

It is relevant to note that UHR participants are usually experiencing subjective distress and are therefore motivated to take part in the clinical research assessment. Similarly, their family members typically encourage them to participate and are readily engaged in the assessment process.

Process to Document Consent

For all subjects, written informed consent will be obtained using consent forms that are approved by the Northwestern University Institutional Review Board (IRB) after the procedures are fully explained. For the Zoom follow up, if the participant chooses to complete the follow up interview online, the consent form will be e-signed on Qualtrics during a phone call or Zoom call with an IRB approved staff member. The vast majority of the patients potentially eligible for this program will have the capacity to consent, as this program involves outpatients who are active

participants in their own health care decisions. We will use the following procedures with potential participants to ensure comprehension of the information provided in the informed consent forms. A staff member will help each subject read the consent form and discuss the content point-by-point. Potential participants will be asked to paraphrase each section to insure comprehension of the content. Indicators that a participant cannot currently comprehend meaningfully the content of the consent form will include: (1) the potential participant has severe formal thought disorder that does not allow him or her to ask understandable questions about the program or to paraphrase the basic points in the consent form; (2) the potential participant is unable to maintain attention to the description of the consent form long enough to perceive the individual basic points in the consent from; (3) the potential participant cannot ask questions or respond sufficiently to indicate agreement due to symptoms like catatonia; and (4) the potential participant expresses delusions related to the program that distort significantly his or her basic understanding of the nature of the research. On the other hand, some of the indicators that the potential participant can, at the time of approach, provide meaningful consent to participate will include: (1) ability to pay attention well enough to read the form or have it read and described to them; (2) ability to paraphrase the basic points in the consent form; and (3) ability to ask reasonable questions about the research and associated treatment conditions. For patient participants, comprehension of the informed consent form will be evaluated by administering an IRB-approved questionnaire about the content of the consent forms. Participants who are unable to demonstrate comprehension of the informed consent on the basis of this evaluation will not be enrolled. All participants are informed that they can request breaks as needed, or withdraw from the study at any time.

Signed consent forms will be stored in a locked filing cabinet in the PI's laboratory, (the ADAPT Lab). Zoom online consent forms will be stored on Qualtrics, only available to IRB approved study staff. All data from questionnaires will be stored on password protected computers and on the PI's password protected server, both of which are only accessible to research staff. To further ensure participants' confidentiality, all participant data (non-contact information) will be identified with a unique research subject identifier. The study team will generate a single master list linking numbers to names and other contact information for the purpose of scheduling and completing follow-up assessments. Zoom interview video recordings will be saved locally on encrypted hard drives in lockboxes. Only ADAPT research assistants who have received IRB approval to work on this project will have access to this master link file and only for the purpose of scheduling follow-up appointments or assessments. This master list as well as all identifying contact information will be destroyed at the conclusion of the final round of data collection. At that point, all data files will be identifiable only by each participant's unique number. After the destruction of identifying information, it will be virtually impossible to link a participant's identity with any of the data she provided during her enrollment in the study.

If the content of the consent forms change, currently enrolled participants will be informed with a document outlining the changes since they initially signed the consent form for the study. Participants will be taken through the changes in person with a lab manager at their next visit to the lab using the document outlining consent changes.

VI. References

ACSM American fitness index ranks 50 largest metro areas on health and community fitness (2011). Last Accessed 5/20/2013 from, http://www.acsm.org/about-acsm/media-room/acsm-in-the-news/2011/08/01/acsm-american-fitness-index-ranks-50-largest-metro-areas-on-health-and-community-fitness

Addington, D., Addington, J., Schissel, B. (1990). A depression rating scale for schizophrenics. Schizophrenia Research 3; 247-251.

America's 15 most active cities (2011). Time Magazine. Accessed 5/27/2013 from http://healthland.time.com/2011/02/18/americas-15-most-active-cities/photo/denver/

Aimone JB, Wiles JGage FH (2006). Potential role for adult neurogenesis in the encoding of time in new memories. *Nat Neurosci* 9, 723-7.

Allen P, Seal ML, Valli I, Fusar-Poli P, Perlini C, Day F, Wood SJ, Williams SCMcguire PK (2011). Altered prefrontal and hippocampal function during verbal encoding and recognition in people with prodromal symptoms of psychosis. *Schizophrenia Bulletin* 37, 746-56.

Amminger GP, Schafer MR, Papageorgiou K, Klier CM, Cotton SM, Harrigan SM, Mackinnon A, Mcgorry PDBerger GE (2010). Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. *Archives of General Psychiatry* 67, 146-54.

Auther AM, Smith CWCornblatt B (2006). *Global Functioning: Social Scale (GF: Social),* New York, Zucker-Hillside Hospital.

Avula CP, Muthukumar AR, Zaman K, Mccarter RFernandes G (2001). Inhibitory effects of voluntary wheel exercise on apoptosis in splenic lymphocyte subsets of C57BL/6 mice. *J Appl Physiol* 91, 2546-52.

Barlati S, De Peri L, Deste G, Fusar-Poli PVita A (2012). Cognitive remediation in the early course of schizophrenia: a critical review. *Curr Pharm Des* 18, 534-41.

Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol, 56*(6), 893-897.

Becker S (2005). A computational principle for hippocampal learning and neurogenesis. *Hippocampus* 15, 722-38.

Benoit A, Bodnar M, Malla AK, Joober RLepage M (2012). The structural neural substrates of persistent negative symptoms in first-episode of non-affective psychosis: a voxel-based morphometry study. *Front Psychiatry* 3, 42.

Berle JO, Hauge ER, Oedegaard KJ, Holsten FFasmer OB (2010). Actigraphic registration of motor activity reveals a more structured behavioural pattern in schizophrenia than in major depression. *BMC Res Notes* 3, 149.

Borg, G. (1998). Borg's perceived exertion and pain scales. Champaign, IL: Human Kinetics.

Brewer WJ, Francey SM, Wood SJ, Jackson HJ, Pantelis C, Phillips LJ, Yung AR, Anderson VAMcgorry PD 2005. Memory impairments identified in people at ultra-high risk for psychosis who later develop first-episode psychosis. *American Journal of Psychiatry.*

Buchan DS, Young JD, Simpson AD (2012). The effects of a novel high intensity exercise intervention on established markers of cardiovascular disease and health in Scottish adolescent youth. J Public Health Res.

Bunce DMurden F (2006). Age, aerobic fitness, executive function, and episodic memory. *European journal of Cognitive Psychology* 18, 221-233.

Cannon TD, Cadenhead K, Cornblatt B, Woods SW, Addington J, Walker E, Seidman LJ, Perkins D, Tsuang M, Mcglashan THeinssen R (2008). Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Archives of General Psychiatry* 65, 28-37.

Cohen J (1988). *Statistical power analyses for the behavioral sciences,* Hillsdale, NJ, Lawrence Erlbaum.

Cohen J, Cohen P, West SAiken L (2003). *Applied multiple regression/correlational analysis for the behavioral sciences,* Hillsdale, NJ, Erlbaum.

Cohen RA, Moser DJ, Clark MM, Aloia MS, Cargill BR, Stefanik S, Albrecht A, Tilkemeier PForman DE (1999). Neurocognitive functioning and improvement in quality of life following participation in cardiac rehabilitation. *Am J Cardiol* 83, 1374-8.

Colcombe SJ, Kramer AF, Erickson KI, Scalf P, Mcauley E, Cohen NJ, Webb A, Jerome GJ, Marquez DXElavsky S (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci U S A* 101, 3316-21.

Cooper DM, Weiler-Ravell D, Whipp BJWasserman K (1984). Aerobic parameters of exercise as a function of body size during growth in children. *J Appl Physiol* 56, 628-34.

Corcoran C, Walker E, Huot R, Mittal VA, Tessner K, Kestler LMalaspina D (2003). The stress cascade and schizophrenia: etiology and onset. *Schizophrenia Bulletin* 29, 671-92. PMID: 14989406

Corcoran CM, First MBCornblatt B (2010). The psychosis risk syndrome and its proposed inclusion in the DSM-V: A risk-benefit analysis. *Schizophrenia Research* 120, 16-22.

Cornblatt B, Green M, Walker EFMittal VA 2008. Schizophrenia: Etiology and Neurocognition. *In:* MILLON, T., BLANEY, P. H. & DAVIS, R. D. (eds.) *Oxford Textbook of Psychopathology.* 2 ed. New York: Oxford University Press.

Cornblatt BA, Auther AM, Niendam T, Smith CW, Zinberg J, Bearden CECannon TD (2007). Preliminary findings for two new measures of social and role functioning in the prodromal phase of schizophrenia. *Schizophrenia Bulletin* 33, 688-702.

Costigan SA, Barnett L, Plotnikoff RCLubans DR (in press). The Health Indicators Associated With Screen-Based Sedentary Behavior Among Adolescent Girls: A Systematic Review. *Journal of Adolescscent Health*.

Costigan SA, Eather A, Plotnikoff RC, Taaffe DR, Lubans DR (2015). High-Intensity Interval Training for Improving Health-Related Fitness in Adolescents: a Systemic Review and Meta-Analysis. *British Journal of Sports Medicine Online* 0, 1-9.

Cotman CWBerchtold NC (2002). Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends Neurosci* 25, 295-301.

Czyrak, A., Mackowiak, M., Chocyk, A., Fijal, K., & Wedzony, K. (2003). Role of glucocorticoids in the regulation of dopaminergic neurotransmission. *Pol J Pharmacol, 55*(5), 667-674.

Deighton, S., & Addington, J. (2013). Exercise practices in individuals at clinical high risk of developing psychosis. *Early intervention in psychiatry*.

De Jong LW, Van Der Hiele K, Veer IM, Houwing JJ, Westendorp RG, Bollen EL, De Bruin PW, Middelkoop HA, Van Buchem MAVan Der Grond J (2008). Strongly reduced volumes of putamen and thalamus in Alzheimer's disease: an MRI study. *Brain* 131, 3277-85.

Dickey CC, Mccarley RWShenton ME (2002). The brain in schizotypal personality disorder: a review of structural MRI and CT findings. *Harv Rev Psychiatry* 10, 1-15.

Dickey CC, Mccarley RW, Voglmaier MM, Niznikiewicz MA, Seidman LJ, Hirayasu Y, Fischer I, Teh EK, Van Rhoads R, Jakab M, Kikinis R, Jolesz FAShenton ME (1999). Schizotypal personality disorder and MRI abnormalities of temporal lobe gray matter. *Biological Psychiatry* 45, 1393-402.

Eastvold AD, Heaton RKCadenhead KS 2007. Neurocognitive deficits in the (putative) prodrome and first episode of psychosis. *Schizophrenia Research.*

Ekelund U, Luan J, Sherar LB, Esliger DW, Griew P, Cooper AInternational Children's Accelerometry Database C (2012). Moderate to vigorous physical activity and sedentary time and cardiometabolic risk factors in children and adolescents. *Journal of the American Medical Association* 307, 704-12.

Ekkekakis P, Lind E, Hall EEPetruzzello SJ (2008). Do regression-based computer algorithms for determining the ventilatory threshold agree? *J Sports Sci* 26, 967-76.

Ekkekakis P, Parfitt GPetruzzello SJ (2011). The pleasure and displeasure people feel when they exercise at different intensities: decennial update and progress towards a tripartite rationale for exercise intensity prescription. *Sports medicine* 41, 641-71.

Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, Kim JS, Heo S, Alves H, White SM, Wojcicki TR, Mailey E, Vieira VJ, Martin SA, Pence BD, Woods JA, Mcauley EKramer AF (2011). Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A* 108, 3017-22.

Etnier JL, Whitwer SS, Landers DM, Petruzzello SJSalazar W (1996). Changes in electroencephalographic activity associated with learning a novel motor task. *Res Q Exerc Sport* 67, 272-9.

Farmer J, Zhao X, Van Praag H, Wodtke K, Gage FHChristie BR (2004). Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo. *Neuroscience* 124, 71-9.

Farrow TF, Hunter MD, Wilkinson ID, Green RDSpence SA (2005). Structural brain correlates of unconstrained motor activity in people with schizophrenia. *Br J Psychiatry* 187, 481-2.

FDA (2015). Tattoos and Permanent Makeup: Fact Sheet. http://www.fda.gov/Cosmetics/ProductsIngredients/Products/ucm108530.htm

Faul F, Erdfelder E, Lang AGBuchner A (2007). G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* 39, 175-91.

Fisher M, Holland C, Merzenich MMVinogradov S (2009). Using neuroplasticity-based auditory training to improve verbal memory in schizophrenia. *American Journal of Psychiatry* 166, 805-11.

Fisher M, Loewy R, Hardy K, Schlosser DVinogradov S (2013). Cognitive Interventions Targeting Brain Plasticity in the Prodromal and Early Phases of Schizophrenia. *Annual Review of Clinical Psycholology*.

Fusar-Poli P, Borgwardt S, Crescini A, Deste G, Kempton MJ, Lawrie S, Guire PMSacchetti E (2011). Neuroanatomy of vulnerability to psychosis: A voxel-based meta-analysis. *Neuroscience and biobehavioral reviews* 35, 1175-1185.

Fusar-Poli P, Deste G, Smieskova R, Barlati S, Yung AR, Howes O, Stieglitz RD, Vita A, Mcguire PBorgwardt S (2012). Cognitive functioning in prodromal psychosis: a meta-analysis. *Archives of General Psychiatry* 69, 562-71.

Fusar-Poli P, Perez J, Broome M, Borgwardt S, Placentino A, Caverzasi E, Cortesi M, Veggiotti P, Politi P, Barale FMcguire P (2007). Neurofunctional correlates of vulnerability to psychosis: a systematic review and meta-analysis. *Neuroscience and biobehavioral reviews* 31, 465-84.

Gallup Poll (2013). Boulder remains least obese U.S. Metro area. Last Accessed 5/24/2013 from http://www.gallup.com/poll/161717/boulder-remains-least-obese-metro-area.aspx.

Gerbino-Rosen G, Roofeh D, Tompkins DA, Feryo D, Nusser L, Kranzler H, Napolitano B, Frederickson A, Henderson I, Rhinewine JKumra S (2005). Hematological adverse events in clozapine-treated children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry* 44, 1024-31.

Gold JM, Barch DM, Carter CS, Dakin S, Luck SJ, Macdonald AW, 3rd, Ragland JD, Ranganath C, Kovacs I, Silverstein SMStrauss M (2012). Clinical, functional, and intertask correlations of measures developed by the Cognitive Neuroscience Test Reliability and Clinical Applications for Schizophrenia Consortium. *Schizophrenia Bulletin* 38, 144-52.

Gomes Da Silva S, Dona F, Da Silva Fernandes MJ, Scorza FA, Cavalheiro EAArida RM (2010). Physical exercise during the adolescent period of life increases hippocampal parvalbumin expression. *Brain Dev* 32, 137-42.

Gorczynski PFaulkner G (2010). Exercise therapy for schizophrenia. *Schizophrenia Bulletin* 36, 665-6.

Gormley SE, Swain DP, High R, Spina RJ, Dowling EA, Kotipalli USGandrakota R (2008). Effect of intensity of aerobic training on VO2max. *Med Sci Sports Exerc* 40, 1336-43.

Gould E, Beylin A, Tanapat P, Reeves AShors TJ (1999). Learning enhances adult neurogenesis in the hippocampal formation. *Nat Neurosci* 2, 260-5.

Green MFNuechterlein KH (2004). The MATRICS initiative: developing a consensus cognitive battery for clinical trials. *Schizophrenia Research* 72, 1-3.

Hardy, C. J., & Rejeski, W. J. (1989). Not what, but how one feels: The measurement of affect during exercise. Journal of Sport and Exercise Psychology, 11, 304-317.

Haroun N, Dunn L, Haroun ACadenhead KS (2006). Risk and protection in prodromal schizophrenia: ethical implications for clinical practice and future research. *Schizophrenia Bulletin* 32, 166-78.

Hickson RC, Foster C, Pollock ML, Galassi TMRich S (1985). Reduced training intensities and loss of aerobic power, endurance, and cardiac growth. *J Appl Physiol* 58, 492-9.

Hillman CH, Erickson KIKramer AF (2008). Be smart, exercise your heart: exercise effects on brain and cognition. *Nature reviews. Neuroscience* 9, 58-65.

Hollenberg M, Ngo LH, Turner DTager IB (1998). Treadmill Exercise Testing in an Epidemiologic Study of Elderly Subjects. *J Gerontol A Biol Sci Med Sci* 53, B259-B267.

Holzschneider K, Wolbers T, Roder BHotting K (2012). Cardiovascular fitness modulates brain activation associated with spatial learning. *Neuroimage* 59, 3003-14.

Howes OD, Montgomery AJ, Asselin MC, Murray RM, Valli I, Tabraham P, Bramon-Bosch E, Valmaggia L, Johns L, Broome M, Mcguire PKGrasby PM (2009). Elevated striatal

dopamine function linked to prodromal signs of schizophrenia. *Archives of General Psychiatry* 66, 13-20.

Hughes JR (1958). Post-tetanic potentiation. *Physiol Rev* 38, 91-113.

Intlekofer KACotman CW (2012). Exercise counteracts declining hippocampal function in aging and Alzheimer's disease. *Neurobiol Dis*.

Janse Van Rensburg K, Taylor A, Hodgson TBenattayallah A (2009). Acute exercise modulates cigarette cravings and brain activation in response to smoking-related images: an fMRI study. *Psychopharmacology* 203, 589-98.

Kim SH, Kim HB, Jang MH, Lim BV, Kim YJ, Kim YP, Kim SS, Kim EHKim CJ (2002). Treadmill exercise increases cell proliferation without altering of apoptosis in dentate gyrus of Sprague-Dawley rats. *Life Science* 71, 1331-40.

Kramer AF, Erickson KIColcombe SJ (2006). Exercise, cognition, and the aging brain. *J Appl Physiol* 101, 1237-42.

Lipska BK (2002). Neonatal disconnection of the rat hippocampus: a neurodevelopmental model of schizophrenia. *Dialogues Clin Neurosci* 4, 361-7.

Logan GRM, Harris N, Duncan S, Schofield G (2014). A Review of Adolescent High-Intensity Interval Training. *Sports Med 44,* 1071-1085.

Maayan LCorrell CU (2010). Management of antipsychotic-related weight gain. *Expert Rev Neurother* 10, 1175-200.

Magnan RE, Kwan, B.M., Ciccolo, J., Gurney, B., & Bryan, A.D. (2013). Aerobic capacity testing with inactive individuals: The role of subjective experience. *J Phys Act Health* 10, 271-279. PMID 22398432

Martin C, Pollock N, Bukstein OLynch K (2000). Inter-rater reliability of the SCID alcohol and substance use disorders section among adolescents. *Drug Alcohol Dependence* 59, 173-176.

Matsuo T, Saotome K, Seino S, Eto M, Shimojo N, Matsushita A, Iemitsu M, Ohshima H, Tanak K, Mukai C (2014). Low-Volume, High-Intensity, Aerobic Interval Exercise for Sedentary Adults: VO2Max, Cardiac Mass and Heart Rate Recovery. *Eur J Appl Physiol 114 (9), 1963-72.*

Mcglashan TH (2006). Is active psychosis neurotoxic? *Schizophrenia Bulletin* 32, 609-13.

Mcglashan TH, Addington J, Cannon T, Heinimaa M, Mcgorry P, O'brien M, Penn D, Perkins D, Salokangas RK, Walsh B, Woods SWYung A (2007). Recruitment and treatment practices for help-seeking "prodromal" patients. *Schizophrenia Bulletin* 33, 715-26.

Mcglashan TH, Zipursky RB, Perkins D, Addington J, Miller TJ, Woods SW, Hawkins KA, Hoffman R, Lindborg S, Tohen MBreier A (2003). The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally symptomatic for psychosis. I. Study rationale and design. *Schizophrenia Research* 61, 7-18.

Mcgorry PD, Yung AR, Phillips LJ, Yuen HP, Francey S, Cosgrave EM, Germano D, Bravin J, Mcdonald T, Blair A, Adlard SJackson H (2002). Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. *Archives of General Psychiatry* 59, 921-8.

Miller TJ, Mcglashan TH, Rosen JL, Cadenhead K, Cannon T, Ventura J, Mcfarlane W, Perkins DO, Pearlson GDWoods SW (2003a). Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive

validity, interrater reliability, and training to reliability. *Schizophrenia Bulletin* 29, 703-15.

Miller TJ, Mcglashan TH, Rosen JL, Somjee L, Markovich PJ, Stein KWoods SW (2002). Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: preliminary evidence of interrater reliability and predictive validity. *American Journal of Psychiatry* 159, 863-5.

Miller TJ, Mcglashan TH, Woods SW, Stein K, Driesen N, Corcoran CM, Hoffman RDavidson L (1999). Symptom assessment in schizophrenic prodromal states. *Psychiatr Q* 70, 273-87.

Miller TJ, Zipursky RB, Perkins D, Addington J, Woods SW, Hawkins KA, Hoffman R, Preda A, Epstein I, Addington D, Lindborg S, Marquez E, Tohen M, Breier AMcglashan TH (2003b). The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally symptomatic for psychosis. II. Baseline characteristics of the "prodromal" sample. *Schizophrenia Research* 61, 19-30.

Mittal VA, Daley M, O'niell J, Bearden CECannon T (2010a). Striatal volumes and dyskinetic movements in youth at high-risk for psychosis. *Schizophrenia Research* 123, 68-70. PMCID: PMC2939316

Mittal VA, Karlsgodt KH, Zinberg J, Cannon TBearden CE (2010b). Identification and Treatment of a Pineal Gland Tumor in an Adolescent with Prodromal Psychotic Symptoms. *American Journal of Psychiatry* 167, 1033-1037. PMID: 20826854

Mittal VA, Neumann C, Saczawa MWalker EF (2008a). Longitudinal progression of movement abnormalities in relation to psychotic symptoms in adolescents at high risk of schizophrenia. *Archives of General Psychiatry* 65, 165-71. PMID: 18250254

Mittal VA, Orr JM, Pelletier A, Dean DJ, Smith ALunsford-Avery J (2013). Hypothalamic-pituitary-adrenal axis dysfunction in non-clinical psychosis. *Psychiatry Research*. PMID 23332683

Mittal VA, Saczawa ME, Walker E, Willhite RWalder D (2008b). Prenatal exposure to viral infection and conversion among adolescents at high-risk for psychotic disorders. *Schizophrenia Research* 99, 375-6. PMCID: PMC2323607

Mittal VA, Tessner KD, Trottman HD, Esterberg M, Dhrub SH, Simeonova DI, Mcmillan AL, Murphy E, Saczawa MEWalker EF (2007). Movement abnormalities and the progression of prodromal symptomatology in adolescents at risk for psychotic disorders. *Journal of Abnormal Psychology* 116, 260-7. PMID: 17516759

Mittal VAWalker EF (2007). Movement abnormalities predict conversion to Axis I psychosis among prodromal adolescents. *Journal of Abnormal Psychology* 116, 796-803. PMID: 18020725

Mittal VAWalker EF (2009). *Movement abnormalities: a putative biomarker of risk for Psychosis,* New York, Springer.

Mittal VAWalker EF (2011a). Abnormal movements and the longitudinal course of role and social functioning in adolescents at high-risk for psychosis. *Schizophrenia Research*. PMID: 21636252

Mittal VAWalker EF (2011b). Minor physical anomalies and vulnerability in prodromal youth. *Schizophrenia Research* 129, 116-21. PMCID: PMC3110506

Mittal VA, Walker EF, Bearden CE, Walder D, Trottman H, Daley M, Simone ACannon TD (2010c). Markers of Basal Ganglia Dysfunction and Conversion to Psychosis:

Neurocognitive Deficits and Dyskinesias in the Prodromal Period. *Biological Psychiatry* 68, 93-99. PMCID: PMC2891189

Mokdad, AH, Marks JS, Stroup DF, Gerberding JL (2004). Acutal causes of death in the United States, 2000. *JAMA* 10;291 1238-1245.

Morrison A, French P, L W, Sw L, A K, J G, S PRp B (2004). Cognitive therapy for the prevention of psychosis in people at ultra-high risk: Randomised controlled trial *Br J Psychiatry* 185, 291-197.

MRI Safety.com (2016). Safety Information Article. http://www.mrisafety.com/SafetyInfov.asp?SafetyInfoID=228

Neves G, Cooke SFBliss TV (2008). Synaptic plasticity, memory and the hippocampus: a neural network approach to causality. *Nature reviews. Neuroscience* 9, 65-75.

Niendam TA, Bearden CE, Johnson JK, Mckinley M, Loewy R, O'brien M, Nuechterlein KH, Green MFCannon TD (2006). Neurocognitive performance and functional disability in the psychosis prodrome. *Schizophrenia Research* 84, 100-11.

Noureddine Y, et al. Experience with magnetic resonance imaging of human subjects with passive implants and tattoos at 7 T: A retrospective study. MAGMA 2015

O'Connor MF et al. (2009). To assess, to control, to exclude: Effects of biobehavioral factors on circulating inflammatory markers. *Brain Behav Immun*

Pajonk FG, Wobrock T, Gruber O, Scherk H, Berner D, Kaizl I, Kierer A, Muller S, Oest M, Meyer T, Backens M, Schneider-Axmann T, Thornton AE, Honer WGFalkai P (2010). Hippocampal plasticity in response to exercise in schizophrenia. *Archives of General Psychiatry* 67, 133-43.

Pantelis C, Velakoulis D, Mcgorry PD, Wood SJ, Suckling J, Phillips LJ, Yung AR, Bullmore ET, Brewer W, Soulsby B, Desmond PMcguire PK (2003). Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *Lancet* 361, 281-8.

Pantelis C, Velakoulis D, Wood SJ, Yucel M, Yung AR, Phillips LJ, Sun DQMcgorry PD (2007). Neuroimaging and emerging psychotic disorders: the Melbourne ultra-high risk studies. *International Review of Psychiatry* 19, 371-81.

Parker BA, Thompson PD, Jordan KC, Grimaldi AS, Assaf M, Jagannathan KPearlson GD (2011). Effect of exercise training on hippocampal volume in humans: a pilot study. *Res Q Exerc Sport* 82, 585-91.

Patenaude B (2007). *FMRIB Technical Report TR07BP1,* London, Oxford.

Pelletier AL, Dean DJ, Lunsford-Avery JR, Smith AK, Orr JM, Gupta T, Millman ZBMittal VA (2013). Emotion recognition and social/role dysfunction in non-clinical psychosis. *Schizophrenia Research* 143, 70-3. PMID: 23182437

Phaneuf SLeeuwenburgh C (2001). Apoptosis and exercise. *Med Sci Sports Exerc* 33, 393-6.

Pimentel AE, Gentile CL, Tanaka H, Seals DRGates PE (2003). Greater rate of decline in maximal aerobic capacity with age in endurance-trained than in sedentary men. *J Appl Physiol* 94, 2406-2413.

Quaney BM, Boyd LA, Mcdowd JM, Zahner LH, He J, Mayo MSMacko RF (2009). Aerobic exercise improves cognition and motor function poststroke. *Neurorehabil Neural Repair* 23, 879-85.

Ragland JD, Ranganath C, Barch DM, Gold JM, Haley B, Macdonald AW, 3rd, Silverstein SM, Strauss ME, Yonelinas APCarter CS (2012). Relational and Item-Specific Encoding

(RISE): task development and psychometric characteristics. *Schizophrenia Bulletin* 38, 114-24.

Rijcken CA, Monster TB, Brouwers JRDe Jong-Van Den Berg LT (2003). Chlorpromazine equivalents versus defined daily doses: how to compare antipsychotic drug doses? *J Clin Psychopharmacol* 23, 657-9.

Rognmo O, Hetland E, Helgerud J, Hoff JSlordahl SA (2004). High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. *Eur J Cardiovasc Prev Rehabil* 11, 216-22.

Ross JR, Matava MJ. Tattoo-induced skin "burn" during magnetic resonance imaging in a professional football player: A case report. Sports Health 2011;3:431-4.

Rosenberger ME, Haskell WL, Albinali F, Mota S, Nawyn JIntille S (in press). Estimating Activity and Sedentary Behavior from an Accelerometer on the Hip or Wrist. *Med Sci Sports Exerc*.

Schafer JLGraham JW (2002). Missing data: our view of the state of the art. *Psychol Methods* 7, 147-77.

Schneider MCooper DM (2011). Enjoyment of exercise moderates the impact of a school-based physical activity intervention. *Int J Behav Nutr Phys Act* 8, 64.

Schneider M, Dunn ACooper D (2009). Affect, exercise, and physical activity among healthy adolescents. *J Sport Exerc Psychol* 31, 706-23.

Seidman LJ, Giuliano AJ, Meyer EC, Addington J, Cadenhead KS, Cannon TD, Mcglashan TH, Perkins DO, Tsuang MT, Walker EF, Woods SW, Bearden CE, Christensen BK, Hawkins K, Heaton R, Keefe RSE, Heinssen R, Cornblatt BAGroup NaPLSN (2010). Neuropsychology of the prodrome to psychosis in the NAPLS consortium: relationship to family history and conversion to psychosis. *Archives of General Psychiatry* 67, 578-88.

Sporn A, Greenstein D, Gogtay N, Sailer F, Hommer DW, Rawlings R, Nicolson R, Egan MF, Lenane M, Gochman P, Weinberger DRRapoport JL (2005). Childhood-onset schizophrenia: smooth pursuit eye-tracking dysfunction in family members. *Schizophrenia Research* 73, 243-52.

Squire LR (1992). Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychological Review* 99, 195-231.

Stroth S, Hille K, Spitzer MReinhardt R (2009). Aerobic endurance exercise benefits memory and affect in young adults. *Neuropsychol Rehabil* 19, 223-43.

Svebak, S., & Murgatroyd, S. (1985). Metamotivational dominance: A multimethod validation of reversal theory constructs. Journal of Personality and Social Psychology, 48(1), 107-116.

Tope WD, Shellock FG. Magnetic resonance imaging and permanent cosmetics (tattoos): Survey of complications and adverse events. J Magn Reson Imag 2002;15:180-184.

United States Census Bureau. (2008). 2006-2008 American Community Survey 3-Year Estimates. Retrieved 8/10, 2010, from http://factfinder.census.gov/servlet/ACSSAFFFacts?_event=ChangeGeoContext&geo_id=16000US0820000&_geoContext=&_street=&_county=Denver&_cityTown=Denver&_state=&_zip=&_lang=en&_sse=on&ActiveGeoDiv=&_useEV=&pctxt=fph&pgsl=010&_submenuId=factsheet_1&ds_name=ACS_2007_3YR_SAFF&_ci_nbr=null&qr_name=null&reg=null%3Anull&_keyword=&_industry=

United States Census-Bureau. (2009). Annual County Resident Population Estimates by Age, Sex, Race, and Hispanic Origin: April 1, 2000 to July 1, 2009. *2009 Population Estimates*.

Uysal N, Tugyan K, Kayatekin BM, Acikgoz O, Bagriyanik HA, Gonenc S, Ozdemir D, Aksu I, Topcu ASemin I (2005). The effects of regular aerobic exercise in adolescent period on hippocampal neuron density, apoptosis and spatial memory. *Neurosci Lett* 383, 241-5.

Valli I, Tognin S, Fusar-Poli PMechelli A (2012). Episodic memory dysfunction in individuals at high-risk of psychosis: a systematic review of neuropsychological and neurofunctional studies. *Curr Pharm Des* 18, 443-58.

Van Uffelen JG, Chin APMJ, Hopman-Rock MVan Mechelen W (2008). The effects of exercise on cognition in older adults with and without cognitive decline: a systematic review. *Clin J Sport Med* 18, 486-500.

Vaynman S, Ying ZGomez-Pinilla F (2004). Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *The European journal of neuroscience* 20, 2580-90.

Voss MW, Erickson KI, Prakash RS, Chaddock L, Kim JS, Alves H, Szabo A, Phillips SM, Wojcicki TR, Mailey EL, Olson EA, Gothe N, Vieira-Potter VJ, Martin SA, Pence BD, Cook MD, Woods JA, Mcauley EKramer AF (2013). Neurobiological markers of exercise-related brain plasticity in older adults. *Brain Behav Immun* 28, 90-9.

Voss MW, Prakash RS, Erickson KI, Basak C, Chaddock L, Kim JS, Alves H, Heo S, Szabo AN, White SM, Wojcicki TR, Mailey EL, Gothe N, Olson EA, Mcauley EKramer AF (2010). Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. *Front Aging Neurosci* 2.

Walder DJ, Mittal VA, Trotman HD, Mcmillan ALWalker EF (2008). Neurocognition and conversion to psychosis in adolescents at high-risk. *Schizophrenia Research* 101, 161-8. PMID: 18280704

WalkerDiforio D (1997). Schizophrenia: a neural diathesis-stress model. *Psychological Review* 104, 667-85.

Walker E, Mittal VA, Tessner K (2008). Stress and the hypothalamic pituitary adrenal axis in the developmental course of schizophrenia. *Annual Review of Clinical Psycholology* 4, 189-216. PMID: 18370616

Walker EF, Brennan PA, Esterberg M, Brasfield J, Pearce BCompton MT (2010). Longitudinal changes in cortisol secretion and conversion to psychosis in at-risk youth. *Journal of Abnormal Psychology* 119, 401-8.

Watson, D., Clark, L. A., & Tellegan, A. (1988). Development and validation of brief measures of positive and negative affect:
The PANAS scales. Journal of Personality and Social Psychology, 54(6), 1063–1070.

Weinberger DR (1995). From neuropathology to neurodevelopment. *Lancet* 346, 552-7.

Wilhelm, I., J. Born, et al. (2007). Is the cortisol awakening rise a response to awakening? Psychoneuroendocrinology. 32: 358-366

White T, Anjum ASchulz SC (2006). The schizophrenia prodrome. *American Journal of Psychiatry* 163, 376-80.

Wible CG, Shenton ME, Hokama H, Kikinis R, Jolesz FA, Metcalf DMccarley RW (1995). Prefrontal cortex and schizophrenia. A quantitative magnetic resonance imaging study. *Archives of General Psychiatry* 52, 279-88.

Wiskott L, Rasch MJKempermann G (2006). A functional hypothesis for adult hippocampal neurogenesis: avoidance of catastrophic interference in the dentate gyrus. *Hippocampus* 16, 329-43.

Wisloff U, Stoylen A, Loennechen JP, Bruvold M, Rognmo O, Haram PM, Tjonna AE, Helgerud J, Slordahl SA, Lee SJ, Videm V, Bye A, Smith GL, Najjar SM, Ellingsen OSkjaerpe T (2007). Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation* 115, 3086-94.

Wolf SA, Melnik AKempermann G (2011). Physical exercise increases adult neurogenesis and telomerase activity, and improves behavioral deficits in a mouse model of schizophrenia. *Brain Behav Immun* 25, 971-80.

Wood SJ, Pantelis C, Proffitt T, Phillips LJ, Stuart GW, Buchanan JA, Mahony K, Brewer W, Smith DJMcgorry PD (2003). Spatial working memory ability is a marker of risk-for-psychosis. *Psychological Medicine* 33, 1239-47.

Woods SW, Breier A, Zipursky RB, Perkins DO, Addington J, Miller TJ, Hawkins KA, Marquez E, Lindborg SR, Tohen MMcglashan TH (2003). Randomized trial of olanzapine versus placebo in the symptomatic acute treatment of the schizophrenic prodrome. *Biological Psychiatry* 54, 453-64.

Wu EQ, Birnbaum HG, Shi L, Ball DE, Kessler RC, Moulis MAggarwal J (2005). The economic burden of schizophrenia in the United States in 2002. *Journal of Clinical Psychiatry* 66, 1122-9.

Yuede CM, Zimmerman SD, Dong H, Kling MJ, Bero AW, Holtzman DM, Timson BFCsernansky JG (2009). Effects of voluntary and forced exercise on plaque deposition, hippocampal volume, and behavior in the Tg2576 mouse model of Alzheimer's disease. *Neurobiol Dis* 35, 426-32.

Yung AR, Yuen HP, Berger G, Francey S, Hung TC, Nelson B, Phillips LMcgorry P (2007). Declining transition rate in ultra high risk (prodromal) services: dilution or reduction of risk? *Schizophrenia Bulletin* 33, 673-81.

Zito JM, Safer DJ, Dosreis S, Gardner JF, Magder L, Soeken K, Boles M, Lynch FRiddle MA (2003). Psychotropic practice patterns for youth: a 10-year perspective. *Archive of Pediatric and Adolescent Medicine* 157, 17-25.